JAMA | Original Investigation

Effect of Tailored Dose-Dense Chemotherapy vs Standard 3-Weekly Adjuvant Chemotherapy on Recurrence-Free Survival Among Women With High-Risk Early Breast Cancer
A Randomized Clinical Trial

Theodoros Foukakis, MD; Gunter von Minckwitz, MD; Nils-Olof Bengtsson, MD; Yvonne Brandberg, PhD; Birgitta Wallberg, MD; Tommy Fornander, MD; Brigitte Mlineritsch, MD; Sabine Schmatloch, MD; Christian F. Singer, MD; Günther Steger, MD; Daniel Egle, MD; Eva Karlsson, MD; Lena Carlsson, MD; Sibylle Loibl, MD; Michael Untch, MD; Mats Hellström, MSc; Hemming Johansson, MSc; Harald Anderson, PhD; Per Malmström, MD; Michael Gnant, MD; Richard Greil, MD; Volker Möbus, MD; Jonas Bergh, MD; for the Swedish Breast Cancer Group (SweBCG), the German Breast Group (GBG), and the Austrian Breast & Colorectal Cancer Study Group (ABCSG)

IMPORTANCE Standard dosing of chemotherapy based on body surface area results in marked interpatient variation in pharmacokinetics, toxic effects, and efficacy. Whether tailored dosing can improve outcomes is unknown, as is the role of dose-dense adjuvant chemotherapy.

OBJECTIVE To determine whether tailored dose-dense adjuvant chemotherapy improves the outcomes of early breast cancer compared with a standard 3-weekly chemotherapy schedule.

DESIGN, SETTING, AND PARTICIPANTS A randomized, open-label, phase 3 trial of women aged 65 years and younger who had surgery for nonmetastatic node-positive or high-risk node-negative breast cancer at 86 sites in Sweden, Germany, and Austria between February 20, 2007, and September 14, 2011.

INTERVENTIONS Patients were randomized 1:1 either to 4 cycles of leukocyte nadir–based tailored and dose-dense adjuvant epirubicin and cyclophosphamide every 2 weeks followed by 4 cycles of tailored dose-dense docetaxel every 2 weeks, or to standard-interval chemotherapy with 3 cycles of fluorouracil and epirubicin-cyclophosphamide every 3 weeks followed by 3 cycles of docetaxel every 3 weeks.

MAIN OUTCOMES AND MEASURES The primary end point was breast cancer recurrence–free survival (BCRFS). Secondary end points included 5-year event-free survival (EFS), distant disease–free survival (DDFS), overall survival (OS), and rates of grade 3 or 4 toxic effects.

RESULTS Among 2017 randomized patients (1006 in the tailored dose-dense group and 1011 in the control group; median [IQR] age, 51 [45-58] years; 80% with hormone receptor–positive tumors; 97% with node-positive disease), 2000 received study treatment (≥1 cycle of chemotherapy; 1001 in the tailored dose-dense group and 999 in the control group). After a median follow-up of 5.3 years (IQR, 4.5-6.1 years), 269 BCRFS events were reported, 118 in the tailored dose-dense group and 151 in the control group (HR, 0.79; 95% CI, 0.61-1.01; log-rank P = .06; 5-year BCRFS, 88.7% vs 85.0%). The tailored dose-dense group had significantly better EFS than the control group (HR, 0.79; 95% CI, 0.63-0.99; P = .04; 5-year EFS, 86.7% vs 82.1%). The groups did not differ in OS (HR, 0.77; 95% CI, 0.57-1.05; P = .09; 5-year OS, 92.1% vs 90.2%) or DDFS (HR, 0.83; 95% CI, 0.64-1.08; P = .17; 5-year DDFS, 89.4% vs 86.7%). Grade 3 or 4 nonhematologic toxic effects occurred in 527 (52.6%) in the tailored dose-dense group and 366 (36.6%) in the control group.

CONCLUSIONS AND RELEVANCE Among women with high-risk early breast cancer, the use of tailored dose-dense chemotherapy compared with standard adjuvant chemotherapy did not result in a statistically significant improvement in breast cancer recurrence–free survival. Nonhematologic toxic effects were more frequent in the tailored dose-dense group.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00798070; isrctn.org Identifier: ISRCTN39017665

JAMA. 2016;316(18):1888-1896. doi:10.1001/jama.2016.15865

Supplemental content

CME Quiz at jamanetworkcme.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A list of the Swedish Breast Cancer Group (SweBCG), German Breast Group (GBG), and Austrian Breast & Colorectal Cancer Study Group (ABCSG) investigators is provided in the eAppendix in Supplement 1.

Corresponding Author: Jonas Bergh, MD, Department of Oncology-Pathology, Cancer Center Karolinska, Karolinska Institutet and University Hospital, 17176 Stockholm, Sweden (jonas.bergh@ki.se).

Breast cancer survival has steadily improved during the past several decades, mainly attributed to the use of adjuvant systemic therapy.[1] The latest meta-analysis of chemotherapy by the Early Breast Cancer Trialists Collaborative Group on 100 000 randomized patients revealed that the proportional reductions in mortality achieved by adjuvant chemotherapy reach up to one-third and are seen in all patient subgroups, irrespective of age, tumor size, nodal status, estrogen receptor status of the tumor, and tamoxifen use.[2]

The Early Breast Cancer Trialists Collaborative Group meta-analysis also demonstrated that higher doses of anthracyclines increase the relative effectiveness of adjuvant chemotherapy.[2] However, dose intensification of anthracyclines has been limited by the occurrence of cardiotoxic effects and secondary hematologic malignant neoplasms at high cumulative doses. Dose-dense therapy, defined as delivery of chemotherapy at shorter intervals without increasing the cumulative dose, was thus suggested as a means to improve efficacy.[3] A meta-analysis of clinical trials with dose-dense schedules showed a survival benefit compared with conventional dosing in estrogen receptor–negative tumors.[4]

Dosing of most chemotherapy agents is calculated based on body surface area, which leads to large interpatient variability of drug clearance and marked interpatient differences in toxic effects.[5] Use of adverse effects as a pharmacokinetic surrogate for tailoring chemotherapy dose has been supported by several reports that indicated a positive correlation of efficacy with hematologic toxic effects.[6-8] Tailored chemotherapy has been investigated in both adjuvant and neoadjuvant settings but has not been established in routine care of patients with breast cancer.[9,10]

The combination of these 2 concepts, dose-dense and tailored therapy, was initially tested in a feasibility phase 2 trial of the Swedish Breast Cancer Group.[11] Based on the results of this study, a randomized clinical trial (Pan-European Tailored Chemotherapy [PANTHER] study) was initiated to compare tailored and dose-dense chemotherapy vs standard chemotherapy for patients with high-risk early breast cancer.

Key Points

Question Does administration of adjuvant systemic chemotherapy for women with early-stage breast cancer using a tailored dose-dense algorithm improve breast cancer recurrence–free survival compared with standard dosing algorithms?

Findings In this randomized clinical trial of 2017 women with high-risk early breast cancer aged 65 years and younger, breast cancer recurrence–free survival rates were 88.7% for tailored dose-dense chemotherapy and 85.0% for standard chemotherapy over a median of 5.3 years, a difference that was not statistically significant.

Meaning A tailored dose-dense algorithm did not significantly improve breast cancer recurrence–free survival for women with high-risk early-stage breast cancer.

Methods

Study Design

This was an open-label, randomized, multicenter, phase 3 trial conducted at 86 study sites in Sweden, Germany, and Austria as an academic collaboration between the Swedish Breast Cancer Group, the German Breast Group, and the Austrian Breast & Colorectal Cancer Study Group. The trial protocol (available in Supplement 2) was designed and approved by a steering committee with representatives from all 3 groups and was approved by ethics review boards with jurisdiction for the participating sites and by relevant health authorities in all countries. All patients provided written informed consent before inclusion. An independent data and safety monitoring committee with expertise in clinical trials and biostatistics was established. The study was conducted according to the Declaration of Helsinki and the principles of good clinical practice. Data were collected by the Central Data Center at Karolinska University Hospital in Stockholm, Sweden, and were analyzed as predefined in the study protocol.

Patients

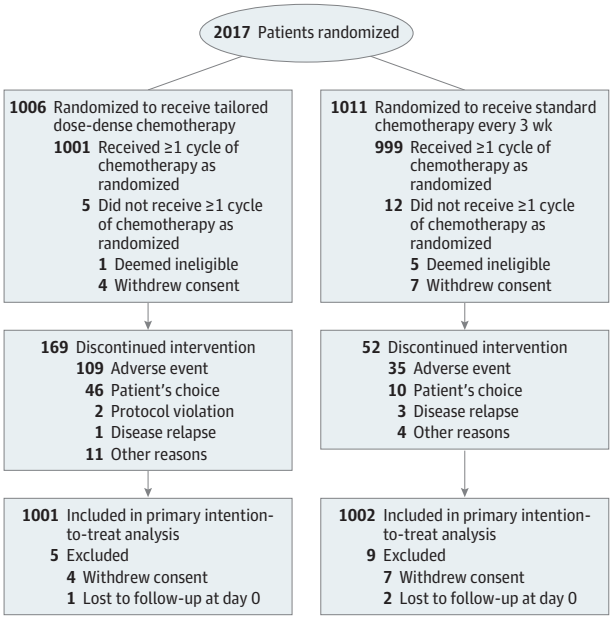
Eligible patients were women aged 18 to 65 years with histologically confirmed, completely resected invasive primary breast cancer that was axillary node positive or high-risk node negative (defined as [1] a tumor that was >2 cm, hormone receptor negative, and histological grade 3; or [2] in a patient aged ≤35 years) without distant metastases. Patients had to have an Eastern Cooperative Oncology Group Performance Status score of 0 or 1 and no major cardiovascular morbidity or other serious medical condition.

Main exclusion criteria were previous adjuvant or neoadjuvant treatment; positive margins after surgery; ongoing pregnancy or lactation; abnormal laboratory values precluding the possibility to safely deliver the cytotoxic agents used in the study; peripheral neuropathy grade 2 or greater; and previous or concurrent malignant neoplasms at other sites, except basal cell carcinoma and/or squamous cell carcinoma in situ of the skin or cervix. Patients with previous contralateral breast cancer diagnosed more than 5 years before registration, not treated with chemotherapy or locoregional radiotherapy, and without objective signs of relapse could be included. Detailed eligibility criteria are listed in the trial protocol in Supplement 2.

Randomization

Randomization was conducted at 1 central office in each country using the permuted block method (block sizes 2, 4, or 6) and was stratified, in addition to country, for center and estrogen receptor status. Patients were randomly assigned 1:1 either to 4 courses of tailored dose-dense epirubicin (38-120 mg/m^2, with starting dose of 90 mg/m^2) and cyclophosphamide (450-1200 mg/m^2, with starting dose of 600 mg/m^2) every 2 weeks followed by 4 courses of tailored dose-dense docetaxel (60-100 mg/m^2, with starting dose of

Figure 1. CONSORT Flow Diagram of a Randomized Trial Comparing Tailored Dose-Dense vs Standard Adjuvant Chemotherapy for High-Risk Early Breast Cancer



CONSORT flow diagram showing the 2003 patients who were included in the intention-to treat analysis. The 2000 patients who received the intervention as randomized (≥1 cycle of chemotherapy; n = 1001 in the tailored dose-dense group and n = 999 in the standard chemotherapy [control] group) were included in the safety population. Information on the number of patients screened for eligibility was not collected and is thus not reported.

75 mg/m^2) every 2 weeks, or to 3 courses of fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (500 mg/m^2) every 3 weeks followed by 3 courses of docetaxel (100 mg/m^2) every 3 weeks. All chemotherapy was administered intravenously. After the completion of tailored dose-dense epirubicin and cyclophosphamide, there was a 3-week interval before the start of tailored dose-dense docetaxel as suggested by the feasibility study,[11] leading to identical total treatment duration in both groups.

Treatment

The dose levels in the experimental group are shown in eTable 1 in Supplement 1 for tailored dose-dense epirubicin and cyclophosphamide and eTable 2 in Supplement 1 for tailored dose-dense docetaxel. Dose tailoring was mainly driven by the nadir values of leukocytes and platelets, evaluated on days 8, 11 or 12, and 14 or 15 after each chemotherapy cycle. Specific nonhematologic toxic effects such as diarrhea grade 3 or greater or stomatitis grade 3 or greater were also dose limiting, as detailed in the dose-tailoring algorithm (eTable 3 in Supplement 1). In the control group, chemotherapy doses were not modified unless severe infection complications, prolonged myelosuppression, or severe toxic effects in the liver occurred (detailed in the trial protocol in Supplement 2).

Bone marrow support with filgrastim (administered subcutaneously once daily on days 4-11) or pegfilgrastim (6 mg administered subcutaneously 24 hours after chemotherapy) was mandatory in the dose-dense group but optional in the control group. After a planned interim safety analysis, primary filgrastim or pegfilgrastim prophylaxis was also recommended (albeit not mandatory) for the control group. Oral ciprofloxacin, 500 mg twice daily, was given on days 5 through 12 as primary prophylaxis during tailored dose-dense epirubicin and cyclophosphamide administration and as secondary prophylaxis following an infection complication during tailored dose-dense docetaxel administration. Mesna was given when cyclophosphamide doses were higher than 1 g/m^2 (eTable 1 in Supplement 1).

Patients with human epidermal growth factor receptor 2 (*HER2*)-positive disease received adjuvant trastuzumab for 1 year either after the completion of chemotherapy or concurrently with taxanes. Following a report from the North Central Cancer Treatment Group N9831 trial, the protocol was amended in October 2007 and recommended trastuzumab concurrently with docetaxel for all patients with *HER2*-positive disease.[12]

Adjuvant endocrine therapy with tamoxifen or aromatase inhibitors was given for at least 5 years to all patients with hormone receptor-positive disease and was started after completion of chemotherapy. Ovarian function suppression with the addition of a gonadotropin-releasing hormone agonist was considered for patients who continued to menstruate after chemotherapy.

Postoperative locoregional radiotherapy was administered after the completion of chemotherapy and no later than 6 weeks after the last course, according to local guidelines. After the end of study treatment, the protocol stipulated follow-up with clinical visits, hematologic and biochemical tests, and yearly mammograms (detailed in the trial protocol in Supplement 2).

Outcomes

The primary end point was breast cancer recurrence-free survival (BCRFS), defined as time from randomization to local, regional, or distant breast cancer relapse or to death due to breast cancer. Secondary efficacy end points included distant disease-free survival (DDFS; time from randomization to distant metastases or death due to breast cancer), event-free survival (EFS; time from randomization to breast cancer relapse, contralateral breast cancer, other malignant neoplasms, or death from any cause), and overall survival (OS; time from randomization to death from any cause). For event-free patients in any of the defined efficacy end points, time was calculated from the date of randomization to the date of the last visit.

Safety was also a secondary end point and was assessed throughout the study treatment according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. The patients were asked to complete assessments of health-related quality of life (HRQoL) at baseline before randomization, after 6 weeks (cycle 3 or 4), and at the end of treatment (cycle 6 or 8). The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life 30-item Core Questionnaire (EORTC QLQ-C30) and

the EORTC Quality of Life 23-item Breast Cancer-Specific Module (EORTC QLQ-BR-23) were used.[13,14] All items in the EORTC QLQ-C30 and QLQ-BR-23 were linearly transformed to functioning or symptom scales ranging from 0 to 100 according to the scoring manual.[15]

Protocol-specified exploratory end points included the evaluation of BCRFS in biological subgroups defined by estrogen receptor status, *HER2* status, and proliferation rate.

Statistical Analysis

The original statistical design of the study (September 2004) aimed at detecting a 10% absolute increase in 5-year BCRFS, from 70% to 80%, with the tailored dose-dense schedule with 80% power, which would require approximately 150 events after 5 years, assuming proportional hazards.[16] This was translated to 450 patients per treatment group. In July 2008, the study was amended to have 80% power to detect smaller differences in 5-year BCRFS (difference of 8%, from 71% to 79%), requiring 225 events. To reach this, a total of 1524 patients were needed, which was deemed feasible because the German Breast Group joined the study. A preplanned blinded interim analysis by the study statistician in cooperation with the independent data and safety monitoring committee in August 2010 revealed that the observed event rate was lower than assumed, and increasing the number of patients to 2000 was advised.

The median follow-up time was estimated using the reversed Kaplan-Meier method.[17] Time to event was estimated and plotted using nonparametric cumulative incidence functions, taking into account the competing risk of deaths not due to breast cancer in the analysis of BCRFS and DDFS. End point-specific survival corresponds to the complement (1 – cumulative incidence function) of these failure curves. Differences in survival times were tested using the log-rank test stratified for site and hormone receptor status. The significance level for BCRFS was set to .05. Effect of allocated treatment on survival was estimated using proportional hazards regression stratified for site and hormone receptor status and is presented as hazard ratio (HR) and 95% confidence interval. For subgroup analyses, tests of interaction were performed by including a product (treatment × factor) in the regression model. Forest plots were used to summarize these results. All efficacy analyses were performed in the intention-to-treat population. No correction for multiple testing was done for the secondary end points and the subgroup analyses; accordingly, these should be considered exploratory.

Safety was assessed in all patients who received at least 1 dose of the study treatment. Grade 3 and 4 hematologic and nonhematologic toxic effects were summarized using descriptive statistics, separately for each chemotherapy regimen.

Patients' HRQoL at the end of study treatment was analyzed using linear regression models including baseline values, country, and treatment. Results are presented as mean difference with 95% confidence interval. *P* values from these analyses refer to Wald tests.

All *P* values are 2-sided. The statistical analyses were done with Stata version 14 statistical software (StataCorp LP).

Table 1. Baseline Characteristics of the Patients Included in the Efficacy Analysis According to Treatment Assignment[a]

Characteristic	Treatment Group, No. (%)[b]	
	Tailored Dose-Dense Chemotherapy (n = 1001)	Standard Chemotherapy (n = 1002)
Age, median (range), y[c]	51.1 (23.3-69.2)	50.3 (21.4-68.6)
Menopausal status		
Premenopausal	515 (51.4)	521 (52.0)
Postmenopausal ≤5 y	162 (16.2)	169 (16.9)
Postmenopausal >5 y	279 (27.9)	267 (26.6)
Unknown or uncertain	45 (4.5)	45 (4.5)
Type of surgery		
Mastectomy	460 (46.0)	472 (47.1)
Breast-conserving surgery	541 (54.0)	530 (52.9)
Tumor size, cm		
≤2	415 (41.5)	413 (41.2)
>2 to 5	507 (50.6)	520 (51.9)
>5	76 (7.6)	68 (6.8)
Missing	5 (0.5)	1 (0.1)
Positive nodes, No.		
0	31 (3.1)	30 (3.0)
1-3	591 (59.0)	555 (55.4)
4-9	263 (26.3)	290 (28.9)
>9	116 (11.6)	127 (12.7)
Tumor grade		
1	59 (5.9)	54 (5.4)
2	484 (48.4)	512 (51.1)
3	453 (45.3)	435 (43.4)
Missing	5 (0.5)	1 (0.1)
Hormone receptor status		
ER or PR positive	805 (80.4)	795 (79.3)
ER and PR negative	195 (19.5)	206 (20.6)
Missing	1 (0.1)	1 (0.1)
HER2 status		
Negative	841 (84.0)	820 (81.8)
Positive	159 (15.9)	182 (18.2)
Missing	1 (0.1)	0
Ki-67-positive cells, %[d]		
≤20	294 (29.4)	294 (29.3)
>20	322 (32.2)	341 (34.0)
Missing	385 (38.5)	367 (36.6)

Abbreviations: ER, estrogen receptor; *HER2*, human epidermal growth factor receptor 2 gene; PR, progesterone receptor.

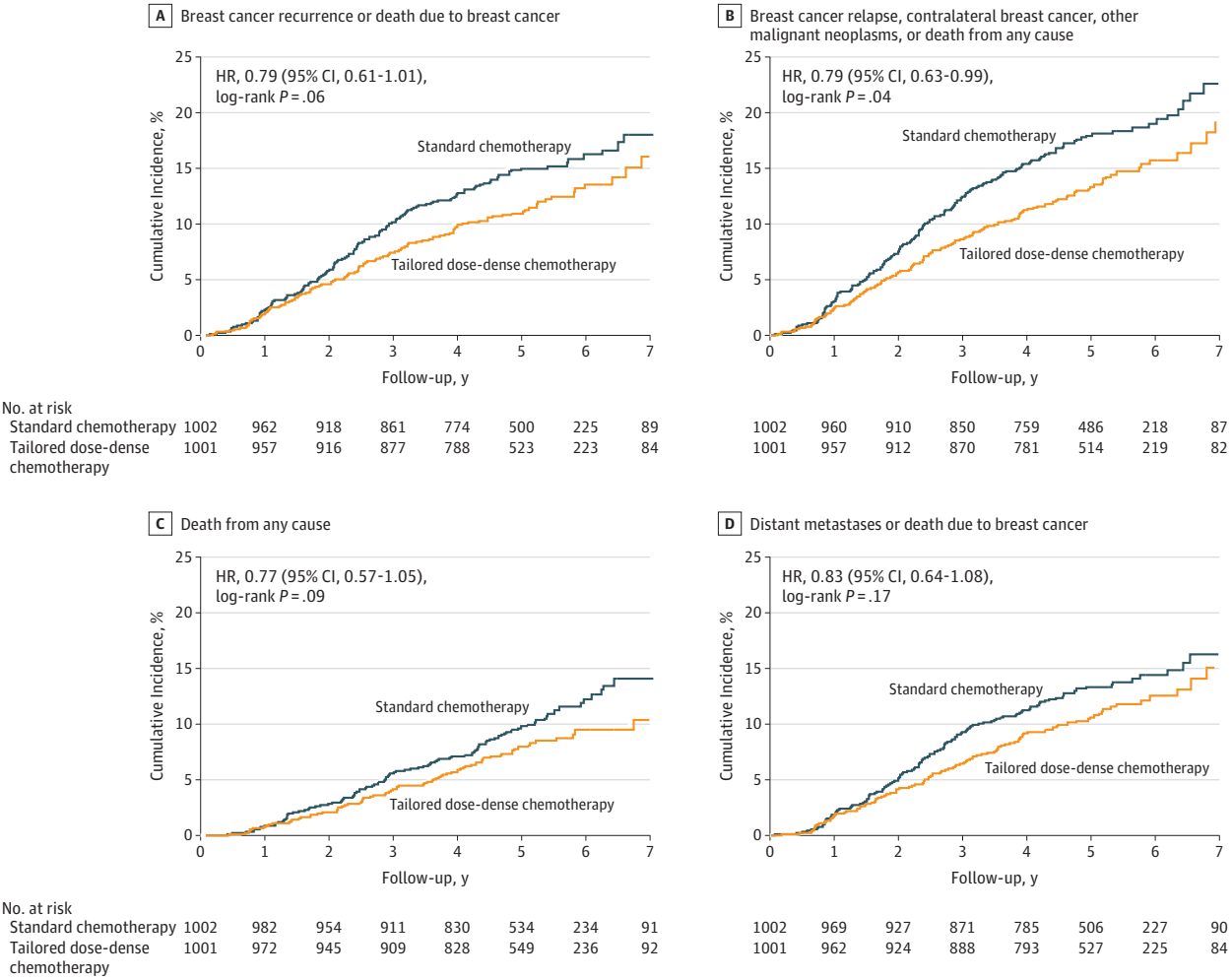
[a] Fourteen included patients did not have complete surgery at enrollment, 9 in the tailored dose-dense group and 5 in the standard chemotherapy group (1 had distant relapse during follow-up). Four (2 in each group) had stage IV disease.

[b] Tailored dose-dense chemotherapy was 4 courses of tailored dose-dense epirubicin and cyclophosphamide every 2 weeks followed by 4 courses of tailored dose-dense docetaxel every 2 weeks. Standard chemotherapy (control group) was 3 courses of fluorouracil, epirubicin, and cyclophosphamide every 3 weeks followed by 3 courses of docetaxel every 3 weeks.

[c] Eighteen patients (8 in the tailored dose-dense group and 10 in the standard chemotherapy group) were older than 65 years at inclusion, as the age limit was misinterpreted as biological rather than chronological age by some investigators.

[d] A marker of cell proliferation, assessed by immunohistochemistry.

Figure 2. Cumulative Incidence Curves of Efficacy End Points in the Intention-to-Treat Population



Cumulative incidence curves are shown for the end point for breast cancer recurrence-free survival (primary end point) (A), the end point for event-free survival (B), the end point for overall survival (C), and the end point for distant disease-free survival (D) after a median follow-up of 5.3 years (interquartile range, 4.5-6.1 years) in the tailored dose-dense group and the standard chemotherapy (control) group. HR indicates hazard ratio.

Results

Patients

Between February 20, 2007, and September 14, 2011, a total of 2017 patients (1006 in the tailored dose-dense group and 1011 in the control group; median [interquartile range] age, 51 [45-58] years; 80% with hormone receptor-positive tumors; 97% with node-positive disease) were enrolled at 86 sites in Sweden (n = 780), Germany (n = 772), and Austria (n = 465). Of these, 11 patients withdrew consent shortly after randomization and 3 additional patients were lost to follow-up at day 0; they were not included in the intention-to-treat population (**Figure 1**). Baseline characteristics were well balanced between the study groups (**Table 1**). A total of 2000 patients (1001 in the tailored dose-dense group and 999 in the control group) received at least 1 course of therapy.

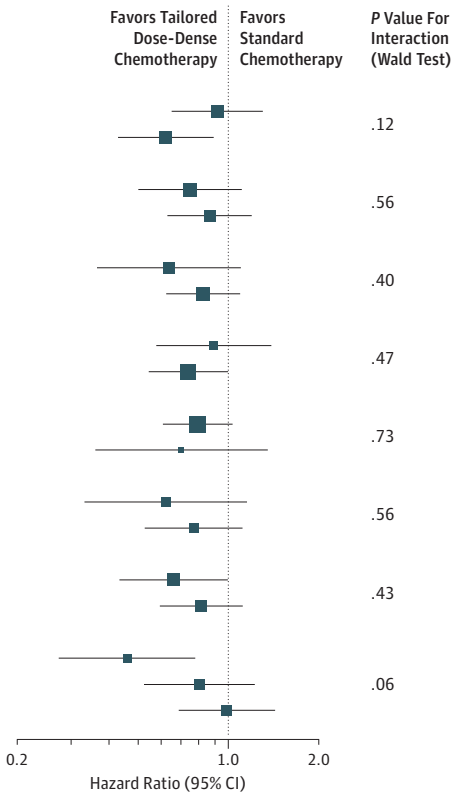
Efficacy

The majority of patients in the tailored dose-dense group (832 of 1001 [83.1%]) and the control group (947 of 999 [94.8%]) received all planned courses of chemotherapy. The difference between the 2 groups is mainly due to the fact that 90 patients (9.0%) in the tailored dose-dense group did not receive the last planned course of docetaxel. The cumulative doses for all study treatments were higher in the tailored dose-dense group, especially for epirubicin and cyclophosphamide (eTable 4 in Supplement 1).

At the data collection cutoff date for this first planned event-driven analysis (January 22, 2016), the median follow-up time was 5.3 years (interquartile range, 4.5-6.1 years). A total of 269 BCRFS events were reported, 118 in the tailored dose-dense group and 151 in the control group (HR, 0.79; 95% CI, 0.61-1.01; log-rank P = .06). Five-year BCRFS was 88.7% in the tailored dose-dense group and 85.0% in the control group

Figure 3. Subgroup Analysis of Breast Cancer Recurrence-Free Survival (BCRFS) Events

Source	Tailored Dose-Dense Chemotherapy: No. of BCRFS Events	Tailored Dose-Dense Chemotherapy: No. of Patients	Standard Chemotherapy: No. of BCRFS Events	Standard Chemotherapy: No. of Patients	Hazard Ratio (95% CI)	*P* Value For Interaction (Wald Test)
Age, y						
<50	62	449	75	486	0.92 (0.65-1.30)	.12
≥50	56	552	76	516	0.62 (0.43-0.89)	
Positive nodes, No.						
0-3	45	622	59	585	0.74 (0.50-1.11)	.56
≥4	73	379	92	417	0.87 (0.63-1.20)	
Tumor size, cm						
≤2	24	413	36	413	0.63 (0.36-1.10)	.40
>2	94	583	114	588	0.82 (0.62-1.10)	
Hormone receptor status						
ER and PR negative	41	195	52	206	0.89 (0.57-1.39)	.47
ER or PR positive	76	805	98	795	0.74 (0.54-1.00)	
HER2 status						
Negative	101	841	124	820	0.79 (0.60-1.03)	.73
Positive	17	159	27	182	0.70 (0.36-1.35)	
Ki-67-positive cells, %						
≤20	19	294	28	294	0.62 (0.33-1.15)	.56
>20	53	322	70	341	0.77 (0.53-1.11)	
Tumor grade						
1 or 2	41	543	61	566	0.66 (0.43-1.00)	.43
3	77	453	89	435	0.81 (0.59-1.12)	
Country						
Austria	23	231	43	230	0.46 (0.27-0.77)	.06
Germany	40	386	50	376	0.80 (0.52-1.23)	
Sweden	55	384	58	396	0.99 (0.68-1.43)	



The size of each box is proportional to the size of the respective subgroup. ER indicates estrogen receptor; *HER2*, human epidermal growth factor receptor 2 gene; and PR, progesterone receptor.

(**Figure 2**A). The tailored dose-dense group had significantly better EFS than the control group (HR, 0.79; 95% CI, 0.63-0.99; *P* = .04; 5-year EFS, 86.7% vs 82.1%; Figure 2B), but the groups did not differ in OS (HR, 0.77; 95% CI, 0.57-1.05; *P* = .09; 5-year OS, 92.1% vs 90.2%; Figure 2C) or DDFS (HR, 0.83; 95% CI, 0.64-1.08; *P* = .17; 5-year DDFS, 89.4% vs 86.7%; Figure 2D). All reported events and first events are detailed in eTable 5 in Supplement 1 and the cumulative incidence of all first events over time is illustrated in eFigure 1 in Supplement 1.

An exploratory subgroup analysis of BCRFS showed that the results were consistent in all prespecified subgroups (**Figure 3**), including patients with hormone receptor-positive disease (HR, 0.74; 95% CI, 0.54-1.00) and hormone receptor-negative disease (HR, 0.89; 95% CI, 0.57-1.39) (Wald test, *P* for interaction = .47). Country was not a predefined factor, but it was included in the analysis (Figure 3). The apparent differences in BCRFS among countries were not significant (*P* for interaction = .06).

Safety

A total of 2000 patients (1001 in the tailored dose-dense group and 999 in the control group) received at least 1 course of therapy and were evaluated for safety. Nonhematologic grade 3 or 4 toxic effects were seen in 527 patients (52.6%) in the tailored dose-dense group and 366 (36.6%) in the control group. The most common grade 3 or 4 adverse events were fatigue, musculoskeletal pain, and neutropenic infection in both groups (**Table 2**). Hematologic toxic effects were increased in the tailored dose-dense group, as was expected owing to dose tailoring, mainly for the tailored dose-dense epirubicin and cyclophosphamide treatment. One toxic death occurred in the control group, caused by reactivation of viral hepatitis B.

During the follow-up, 37 secondary non-breast cancer malignant neoplasms were reported: 18 in the tailored dose-dense group and 19 in the control group (eTable 6 in Supplement 1). These included 5 cases of myelodysplastic syndrome or acute myeloid leukemia: 3 in the tailored dose-dense group and 2 in the control group.

Health-Related Quality of Life

Health-related quality of life was evaluated in 1629 patients who agreed to participate in these assessments. No statistical differences were found at baseline for any of the HRQoL variables. Statistically significant differences were seen between the treatment groups, favoring the control group on 13 of 15 variables on the EORTC QLQ-C30 at the end of treatment (*P* < .01; eFigure 2 and eTable 7 in Supplement 1). For the

Table 2. Number of Patients With Any of the Targeted Grade 3 or 4 Adverse Events According to Treatment Group[a]

Adverse Event[b]	No. (%)					
	Tailored Dose-Dense Chemotherapy		Standard Chemotherapy		Total	
	Epirubicin and Cyclophosphamide (n = 1001)	Docetaxel (n = 948)	Fluorouracil, Epirubicin, and Cyclophosphamide (n = 999)	Docetaxel (n = 980)	Tailored Dose-Dense Chemotherapy (n = 1001)	Standard Chemotherapy (n = 999)
Nonhematologic toxic effects						
Diarrhea	14 (1.4)	33 (3.5)	8 (0.8)	32 (3.3)	44 (4.4)	40 (4.0)
Nausea	42 (4.2)	10 (1.1)	15 (1.5)	7 (0.7)	50 (5.0)	21 (2.1)
Vomiting	32 (3.2)	4 (0.4)	23 (2.3)	3 (0.3)	36 (3.6)	26 (2.6)
Oral mucositis	30 (3.0)	53 (5.6)	9 (0.9)	24 (2.4)	77 (7.7)	33 (3.3)
Neutropenic infection or fever	98 (9.8)	23 (2.4)	79 (7.9)	87 (8.9)	115 (11.5)	154 (15.4)
Infection with normal neutrophil counts	25 (2.5)	74 (7.8)	30 (3.0)	37 (3.8)	94 (9.4)	65 (6.5)
Pain	26 (2.6)	109 (11.5)	12 (1.2)	112 (11.4)	127 (12.7)	123 (12.3)
Fatigue	95 (9.5)	162 (17.1)	27 (2.7)	89 (9.1)	216 (21.6)	106 (10.6)
Hand-foot skin reaction[c]	3 (0.3)	91 (9.6)	1 (0.1)	17 (1.7)	92 (9.2)	18 (1.8)
Neuropathy						
Motor	1 (0.1)	17 (1.8)	0	6 (0.6)	18 (1.8)	6 (0.6)
Sensory	2 (0.2)	31 (3.3)	2 (0.2)	11 (1.1)	33 (3.3)	13 (1.3)
Nail changes	0	23 (2.4)	0	6 (0.6)	23 (2.3)	6 (0.6)
Total	269 (26.9)	403 (42.5)	164 (16.4)	277 (28.3)	527 (52.6)	366 (36.6)
Hematologic toxic effects						
Anemia, hemoglobin <80 g/L	37 (3.7)	12 (1.3)	7 (0.7)	6 (0.6)	46 (4.6)	11 (1.1)
Leukopenia, leukocytes <2000/μL	896 (89.5)	145 (15.3)	680 (68.1)	468 (47.8)	908 (90.7)	809 (81.0)
Neutropenia, neutrophils <1000/μL	878 (87.7)	166 (17.5)	854 (85.5)	518 (52.9)	899 (89.8)	908 (90.9)
Thrombocytopenia, platelets $<50 \times 10^3$/μL	41 (4.1)	7 (0.7)	16 (1.6)	3 (0.3)	46 (4.6)	19 (1.9)
Total	935 (93.4)	198 (20.9)	890 (89.1)	551 (56.2)	944 (94.3)	938 (93.9)

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10.0; leukocytes and neutrophils to $\times 10^9$ per liter, multiply by 0.001; and platelets to $\times 10^9$ per liter, multiply by 1.0.

[a] Sample sizes are the numbers of patients who started at least 1 cycle of chemotherapy. Tailored dose-dense chemotherapy was 4 courses of tailored dose-dense epirubicin and cyclophosphamide every 2 weeks followed by 4 courses of tailored dose-dense docetaxel every 2 weeks. Standard chemotherapy (control group) was 3 courses of fluorouracil, epirubicin, and cyclophosphamide every 3 weeks followed by 3 courses of docetaxel every 3 weeks.

[b] Toxic effects were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

[c] Palmar-plantar erythrodysesthesia.

EORTC QLQ-BR-23, patients in the tailored dose-dense group scored worse on the sexual functioning and chemotherapy adverse effects subscales than the control group. Moderate clinical differences (10-19 points) were found for the subscales of global health status, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss, and chemotherapy adverse effects, all favoring the control group. In addition, there were small clinical differences (5-9 points) between the treatment groups for physical functioning, cognitive functioning, insomnia, and diarrhea, with higher levels of HRQoL in the control group.

Discussion

This international, multicenter, randomized phase 3 study compared a tailored and dose-dense schedule vs a standard 3-weekly schedule of adjuvant chemotherapy in axillary lymph node–positive or high-risk lymph node–negative early breast cancer. There was no statistically significant improvement in BCRFS with the tailored dose-dense schedule, and the point estimate difference of 3.7% was less than the 8.0% used in designing the study. In addition, nonhematologic toxic effects were more frequent in the tailored dose-dense group. The statistically significant relative benefit of 21.0% in EFS, a secondary end point in this study, is in the same range as in the meta-analysis of the first-generation trials (19%) and in a more recent trial (23%) comparing dose-dense vs conventional chemotherapy.[4,18]

The investigational scheduling of chemotherapy in this trial used both higher dose density and dose escalation to intensify treatment, similar to a previous study by Moebus et al.[19] Hypothetically, this schedule may increase efficacy both when tumor growth follows Gompertzian kinetics requiring higher density[20] and when partially resistant clones are present, requiring higher doses. Additionally, dose escalation was achieved in a controlled fashion by tailoring chemotherapy doses according to the observed toxic effects in each patient. Dose escalation led, as expected, to a worsening of HRQoL measures during treatment and an increase of grade 3 or 4 adverse effects, but no toxic deaths and no increase in secondary malignant neoplasms. Although the total treatment time

was similar, patients in the tailored dose-dense group underwent more therapy courses and subsequently had more toxic effects, more hospital visits, and frequent blood draws.

The observed 5-year BCRFS for the control group was 85.0%, much higher than the assumed 70% when the trial was designed, despite the fact that 40% of the patients had 4 or more positive axillary nodes. This may be due to the high inclusion of patients with hormone receptor–positive disease, frequent use of granulocyte colony-stimulating factor support, adjuvant trastuzumab for *HER2*-amplified tumors, and optimized endocrine therapy compared with historical cohorts. As suggested by the Eastern Cooperative Oncology Group 1199 trial,[21] an additional advantage may have been the use of 3-weekly docetaxel instead of paclitaxel, which was used in the control group of previous studies of dose-dense therapy.[3,18]

There was no heterogeneity in the effect of therapy intensification among prespecified subgroups, including hormone receptor status and *HER2* status of the primary tumor. An individual patient data meta-analysis would help to assess whether chemotherapy dose intensification in early breast cancer should be reserved for specific subgroups of patients.

The study has some limitations that should be acknowledged. First, the null hypothesis could not be rejected for the primary end point and most of the secondary end points. Longer follow-up could show whether this indicates lack of effect or lack of statistical power due to a better outcome than expected for both groups. Second, although predefined, the described secondary end point and subgroup analyses were not adequately powered and must be considered exploratory. Third, the combination of dose tailoring and dose-dense scheduling does not allow any conclusions about which of the 2 strategies for dose intensification (or both) account for the observed outcomes.

Conclusions

Among women with high-risk early breast cancer, the use of tailored dose-dense chemotherapy compared with standard adjuvant chemotherapy did not result in a statistically significant improvement in BCRFS. Nonhematologic toxic effects were more frequent in the tailored dose-dense group.

ARTICLE INFORMATION

Author Affiliations: Department of Oncology-Pathology, Cancer Center Karolinska, Karolinska Institutet and University Hospital, Stockholm, Sweden (Foukakis, Brandberg, Wallberg, Fornander, Hellström, Johansson, Bergh); German Breast Group (GBG), Neu-Isenburg, Germany (von Minckwitz, Loibl); Norrland University Hospital, Umeå, Sweden (Bengtsson); Landeskrankenhaus and Paracelsus Medical University, Salzburg, Austria (Mlineritsch, Greil); Elisabeth Hospital, Kassel, Germany (Schmatloch); Department of Gynecology, Comprehensive Cancer Center, Medical University, Vienna, Austria (Singer); Department of Internal Medicine, Comprehensive Cancer Center, Medical University, Vienna, Austria (Steger); Department of Gynecology, Medical University, Innsbruck, Austria (Egle); Central Hospital, Karlstad, Sweden (Karlsson); County Hospital, Sundsvall, Sweden (Carlsson); Helios Klinikum, Berlin-Buch, Germany (Untch); Department of Clinical Sciences, Cancer Epidemiology, Lund University, Lund, Sweden (Anderson); Skåne University Hospital, Lund, Sweden (Malmström); Department of Surgery, Comprehensive Cancer Center, Medical University, Vienna, Austria (Gnant); Klinikum Frankfurt Höchst, Frankfurt, Germany (Möbus).

Author Contributions: Drs Foukakis and Bergh had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: von Minckwitz, Bengtsson, Brandberg, Wallberg, Fornander, Mlineritsch, Steger, Carlsson, Loibl, Untch, Anderson, Malmström, Gnant, Bergh.
Acquisition, analysis, or interpretation of data: Foukakis, von Minckwitz, Brandberg, Fornander, Schmatloch, Singer, Steger, Egle, Karlsson, Loibl, Untch, Hellström, Johansson, Malmström, Gnant, Greil, Möbus, Bergh.
Drafting of the manuscript: Foukakis, von Minckwitz, Brandberg, Mlineritsch, Singer, Steger, Karlsson, Loibl, Untch, Bergh.
Critical revision of the manuscript for important intellectual content: Foukakis, von Minckwitz, Bengtsson, Brandberg, Wallberg, Fornander, Schmatloch, Singer, Steger, Egle, Karlsson, Carlsson, Loibl, Untch, Hellström, Johansson, Anderson, Malmström, Gnant, Greil, Möbus, Bergh.
Statistical analysis: Foukakis, Brandberg, Johansson, Anderson.
Obtained funding: von Minckwitz, Steger, Gnant, Bergh.
Administrative, technical, or material support: von Minckwitz, Bengtsson, Wallberg, Fornander, Mlineritsch, Singer, Karlsson, Loibl, Untch, Hellström, Malmström, Gnant, Greil, Möbus, Bergh.
Study supervision: Foukakis, von Minckwitz, Brandberg, Singer, Steger, Loibl, Untch, Malmström, Gnant, Greil, Möbus, Bergh.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Foukakis reported receiving grants from Roche and personal fees from Novartis, Pfizer, Roche, and UpToDate. Dr von Minckwitz reported receiving personal fees from Celgene, Amgen, and Roche. Dr Steger reported receiving personal fees and nonfinancial support from Amgen. Dr Gnant reported receiving grants and personal fees from AstraZeneca, Novartis, Roche, and Pfizer and personal fees from Accelsior, Celgene, GlaxoSmithKline, Amgen, and OBI Pharma. Dr Greil reported receiving grants and personal fees from Amgen, Roche, Novartis, and Takeda; grants from Boehringer Ingelheim, Celgene, and Merck; and personal fees from BMS. Dr Möbus reported receiving personal fees from Amgen, Celgene, Roche, and AstraZeneca. Dr Bergh reported receiving fees to Asklepios Medicin HB from UpToDate and receiving grants to Karolinska Institutet and University Hospital from AstraZeneca, Amgen, Bayer, Merck, Pfizer, Roche, and Sanofi-Aventis. No other disclosures were reported.

Funding/Support: This study was supported by grants from the Swedish Cancer Society to the Karolinska Institutet, from the research funds at Radiumhemmet, and from Amgen, Roche, and Sanofi-Aventis to the Swedish Breast Cancer Group (SweBCG) at Karolinska University Hospital, the German Breast Group (GBG), and the Austrian Breast & Colorectal Cancer Study Group (ABCSG).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Previous Presentation: This study was presented as an oral presentation at the Annual Meeting of the American Society of Clinical Oncology; June 4, 2016; Chicago, Illinois.

Additional Contributions: We are grateful to all patients participating in the Pan-European Tailored Chemotherapy (PANTHER) study, the study monitors, the main data center at Karolinska University Hospital for SweBCG, and the data centers at ABCSG and GBG. Erik Wist, MD, Ullevåls University Hospital, Oslo, Norway, Jan G. M. Klijn, MD, Erasmus Medical Centre, Erasmus University, Rotterdam, the Netherlands, and Anthony Howell, MD, Christie Hospital NHS Foundation Trust, Manchester, England, served as members of the independent data and safety monitoring committee; they were not compensated for their contribution to this study. The study was also designated as a PANTHER study, trial SBG 2004-1 by SweBCG, trial GBG-53 by GBG, and trial ABCSG-25 by ABCSG.

REFERENCES

1. Berry DA, Cronin KA, Plevritis SK, et al; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784-1792.

2. Peto R, Davies C, Godwin J, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379(9814):432-444.

3. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*. 2003;21(8):1431-1439.

4. Bonilla L, Ben-Aharon I, Vidal L, Gafter-Gvili A, Leibovici L, Stemmer SM. Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. *J Natl Cancer Inst*. 2010;102(24):1845-1854.

5. Baker SD, Verweij J, Rowinsky EK, et al. Role of body surface area in dosing of investigational anticancer agents in adults, 1991-2001. *J Natl Cancer Inst*. 2002;94(24):1883-1888.

6. Cameron DA, Massie C, Kerr G, Leonard RC. Moderate neutropenia with adjuvant CMF confers improved survival in early breast cancer. *Br J Cancer*. 2003;89(10):1837-1842.

7. Colleoni M, Price K, Castiglione-Gertsch M, et al; International Breast Cancer Study Group. Dose-response effect of adjuvant cyclophosphamide, methotrexate, 5-fluorouracil (CMF) in node-positive breast cancer. *Eur J Cancer*. 1998;34(11):1693-1700.

8. Saarto T, Blomqvist C, Rissanen P, Auvinen A, Elomaa I. Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer. *Br J Cancer*. 1997;75(2):301-305.

9. Bonnefoi H, Piccart M, Bogaerts J, et al; EORTC 10994/BIG 1-00 Study Investigators. TP53 status for prediction of sensitivity to taxane versus non-taxane neoadjuvant chemotherapy in breast cancer (EORTC 10994/BIG 1-00): a randomised phase 3 trial. *Lancet Oncol*. 2011;12(6):527-539.

10. Wilking N, Lidbrink E, Wiklund T, et al. Long-term follow-up of the SBG 9401 study comparing tailored FEC-based therapy versus marrow-supported high-dose therapy. *Ann Oncol*. 2007;18(4):694-700.

11. Margolin S, Bengtsson NO, Carlsson L, et al; Scandinavian Breast Group Study SBG 2004-1. A randomised feasibility/phase II study (SBG 2004-1) with dose-dense/tailored epirubicin, cyclophoshamide (EC) followed by docetaxel (T) or fixed dosed dose-dense EC/T versus T, doxorubicin and C (TAC) in node-positive breast cancer. *Acta Oncol*. 2011;50(1):35-41.

12. Perez EA, Suman VJ, Davidson NE, et al. Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 2011;29(34):4491-4497.

13. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.

14. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol*. 1996;14(10):2756-2768.

15. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. *EORTC QLQ-C30 Scoring Manual*. 3rd ed. Brussels, Belgium: European Organization for Research & Treatment of Cancer; 2001.

16. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat Med*. 1982;1(2):121-129.

17. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343-346.

18. Del Mastro L, De Placido S, Bruzzi P, et al; Gruppo Italiano Mammella (GIM) Investigators. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. *Lancet*. 2015;385(9980):1863-1872.

19. Moebus V, Jackisch C, Lueck HJ, et al. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol*. 2010;28(17):2874-2880.

20. Norton L. A Gompertzian model of human breast cancer growth. *Cancer Res*. 1988;48(24, pt 1):7067-7071.

21. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med*. 2008;358(16):1663-1671.