Randomized Phase 3 Trial of Fluorouracil, Epirubicin, and Cyclophosphamide Alone or Followed by Paclitaxel for Early Breast Cancer

Miguel Martín, Álvaro Rodríguez-Lescure, Amparo Ruiz, Emilio Alba, Lourdes Calvo, Manuel Ruiz-Borrego, Blanca Munárriz, César A. Rodríguez, Carmen Crespo, Enrique de Alava, José Antonio López García-Asenjo, María Dolores Guitián, Sergio Almenar, Jesús Fernando González-Palacios, Francisco Vera, José Palacios, Manuel Ramos, Jose Manuel Gracia Marco, Ana Lluch, Isabel Alvarez, Miguel Angel Seguí, José Ignacio Mayordomo, Antonio Antón, José Manuel Baena, Arrate Plazaola, Alfonso Modolell, Amadeu Pelegrí, Jose Ramón Mel, Enrique Aranda, Encarna Adrover, José Valero Álvarez, José Luis García Puche, Pedro Sánchez-Rovira, Sonia Gonzalez, José Manuel López-Vega

On behalf of the GEICAM 9906 Study Investigators

Background Taxanes are among the most active drugs for the treatment of metastatic breast cancer, and, as a consequence, they have also been studied in the adjuvant setting.

Methods After breast cancer surgery, women with lymph node–positive disease were randomly assigned to treatment with fluorouracil, epirubicin, and cyclophosphamide (FEC) or with FEC followed by weekly paclitaxel (FEC-P). The primary endpoint of study—5-year disease-free survival (DFS)—was assessed by Kaplan–Meier analysis. Secondary endpoints included overall survival and analysis of the prognostic and predictive value of clinical and molecular (hormone receptors by immunohistochemistry and HER2 by fluorescence in situ hybridization) markers. Associations and interactions were assessed with a multivariable Cox proportional hazards model for DFS for the following covariates: age, menopausal status, tumor size, lymph node status, type of chemotherapy, tumor size, positive lymph nodes, HER2 status, and hormone receptor status. All statistical tests were two-sided.

Results Among the 1246 eligible patients, estimated rates of DFS at 5 years were 78.5% in the FEC-P arm and 72.1% in the FEC arm (difference = 6.4%, 95% confidence interval [CI] = 1.6% to 11.2%; $P = .006$). FEC-P treatment was associated with a 23% reduction in the risk of relapse compared with FEC treatment (146 relapses in the 614 patients in the FEC-P arm vs 193 relapses in the 632 patients in the FEC arm, hazard ratio [HR] = 0.77, 95% CI = 0.62 to 0.95; $P = .022$) and a 22% reduction in the risk of death (73 and 95 deaths, respectively, HR = 0.78, 95% CI = 0.57 to 1.06; $P = .110$). Among the 928 patients for whom tumor samples were centrally analyzed, type of chemotherapy (FEC vs FEC-P) ($P = .017$), number of involved axillary lymph nodes ($P < .001$), tumor size ($P = .020$), hormone receptor status ($P = .004$), and HER2 status ($P = .006$) were all associated with DFS. We found no statistically significant interaction between HER2 status and paclitaxel treatment or between hormone receptor status and paclitaxel treatment.

Conclusions Among patients with operable breast cancer, FEC-P treatment statistically significantly reduced the risk of relapse compared with FEC as adjuvant therapy.

J Natl Cancer Inst 2008;100:805–814

Affiliations of authors: Departments of Medical Oncology (MM) and Pathology (JALGA), Hospital Universitario San Carlos, Madrid, Spain; Department of Medical Oncology, Hospital Universitario de Elche, Elche, Spain (ARL); Departments of Medical Oncology (AR) and Pathology (S. Almenar), Instituto Valenciano de Oncologia, Valencia, Spain; Department of Medical Oncology, Hospital Virgen de la Victoria, Málaga, Spain (E. Alba); Departments of Medical Oncology (LC) and Pathology (MDG), Complejo Hospitalario Juan Canalejo, La Coruña, Spain; Departments of Medical Oncology (MR) and Pathology (JP), Hospital Vírgen del Rocío, Sevilla, Spain; Departments of Medical Oncology (BM) and Pathology (FV), Hospital La Fe, Valencia, Spain; Department of Medical Oncology, Hospital Universitario de Salamanca, Salamanca, Spain (CAR); Departments of Medical Oncology (CC) and Pathology (JFGP), Hospital Ramón y Cajal, Madrid, Spain; Department of Pathology, Centro de Investigación del Cáncer, Salamanca, Spain (E. de Alava); Department of Medical Oncology, Centro Oncológico de Galicia, La Coruña, Spain (MR); Department of Medical Oncology, Hospital de Cabueñes, Gijón, Spain (JMGM); Department of Medical Oncology, Hospital Clínico Universitario de Valencia, Valencia, Spain (AL); Department of Medical Oncology, Hospital de Donostia, San Sebastián, Spain (IA); Department of Medical Oncology, Hospital Parc Taulí, Sabadell, Spain (MAS); Department of Medical Oncology, Hospital Clínico Lozano Blesa, Zaragoza, Spain (JIM); Department of Medical Oncology, Hospital Miguel Servet, Zaragoza, Spain (AA); Department of Medical Oncology, Complejo Hospitalario Puerta del Mar, Cádiz, Spain (JMB); Department of Medical Oncology, Instituto Oncológico de Guipúzcoa, San Sebastián, Spain (A. Plazaola); Department of Medical Oncology, Clínica Corachan, Barcelona, Spain (AM); Department of Medical Oncology, Hospital Universitario San Joan de Reus, Tarragona, Spain

CONTEXT AND CAVEATS

Prior knowledge

Taxanes are among the most active drugs for the treatment of metastatic breast cancer.

Study design

Phase 3 randomized trial among women with lymph node–positive disease evaluating treatment with fluorouracil, epirubicin, and cyclophosphamide (FEC) with FEC followed by weekly paclitaxel (FEC-P).

Contribution

FEC-P treatment statistically significantly reduced the risk of relapse compared with FEC as adjuvant therapy. FEC-P treatment was associated with a statistically significant 23% reduction in the risk of relapse compared with FEC treatment and a non–statistically significant 22% reduction in the risk of death.

Implications

In the adjuvant setting, addition of taxanes to FEC chemotherapy reduces the risk of relapse for patients with lymph node–positive breast cancer.

Limitations

The number of patients evaluated in this trial was small.

(A. Pelegri); Department of Medical Oncology, Complejo Hospitalario Xeral Calde, Lugo, Spain (JMM); Department of Medical Oncology, Hospital Provincial de Córdoba, Córdoba, Spain (E. Aranda); Department of Medical Oncology, Hospital General de Alicante, Alicante, Spain (E. Adrover); Hospital Provincial de Zamora, Zamora, Spain (JVA); Department of Medical Oncology, Hospital San Cecilio de Granada, Granada, Spain (JLGP); Department of Medical Oncology, Hospital Ciudad de Jaén, Jaén, Spain (PSR); Department of Medical Oncology, Mutua de Terrasa, Terrasa, Spain (SG); Department of Medical Oncology, Hospital Universitario Marqués de Valdecilla, Santander, Spain (JMLV).

Correspondence to: Miguel Martín, MD, Servicio de Oncologia Medica, Hospital Universitario San Carlos, Ciudad Universitaria s/n, 28040 Madrid, Spain (e-mail: mmartin@geicam.org).

See "Notes" following "References."

DOI: 10.1093/jnci/djn151

A comprehensive meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (1,2) has demonstrated that chemotherapy (mainly cyclophosphamide, methotrexate, and 5-fluorouracil [CMF]–like regimens) administered after surgery is able to reduce the annual odds of recurrence and death among operable breast cancer patients by 24% and 14%, respectively. In the late 1970s and the 1980s, anthracycline-containing combination treatments were tested as adjuvant therapy in prospective randomized trials and appeared to be statistically significantly more effective in preventing breast cancer relapse and death than CMF chemotherapy (1). The absolute benefit in terms of disease-free survival (DFS) obtained with anthracyclines (doxorubicin or epirubicin) compared with CMF is, however, small (3% at 5 years and 4% at 10 years) (2), and the long-term toxic effects of these drugs, particularly their cardiac toxic effects (3), are important concerns and indicate that anthracycline-containing regimens should be used only for women who are most likely to benefit from them. It has been proposed that the subset of patients who actually benefit from treatment with anthracyclines (as opposed to CMF) are those whose tumors have amplification of the topoisomerase IIα gene (4) or *HER2* gene (5).

Taxanes are among the most active drugs for the treatment of metastatic breast cancer. Several adjuvant therapy trials (6–10) comparing anthracycline-containing chemotherapy with taxane (paclitaxel and docetaxel)-containing regimens (ie, the first-generation taxane trials) showed an absolute improvement in 5-year DFS of 4%–7%. Because taxane-containing regimens are usually even more toxic than the conventional anthracycline-containing regimens and because the benefit is limited to a small percentage of patients, the identification of the subgroup of patients who actually benefit from taxane-containing regimens is crucial. Several attempts (6–8) have been made, largely on the basis of retrospective subset analyses, to identify the molecular characteristics of the breast tumors from the patients who obtain the greatest benefit from taxane treatment. To date, hormone receptor (ie, estrogen and progesterone receptor) and HER2 status are two of the most important molecular factors that are prognostic and could be predictive of response to chemotherapy in early breast cancer (11). A recent study by the Cancer and Leukemia Group B (CALGB) has indicated that patients who obtain the maximum benefit from paclitaxel are those whose tumors overexpress the *HER2* gene (12).

We previously reported (13) the preliminary interim analysis of a first-generation taxane trial, the Grupo Español para la Investigación del Cáncer de Mama (GEICAM [Spanish Group for the Investigation of Breast Cancer]) trial 9906, which evaluated fluorouracil, epirubicin, and cyclophosphamide (FEC) alone vs the taxane-containing combination of FEC followed by weekly paclitaxel (FEC-P). We now present the final results of this study. We also investigate associations between various molecular characteristics and response to taxane treatment.

Patients and Methods

Study Population

Women eligible for the study were aged between 18 and 75 years and had undergone primary curative surgery (ie, mastectomy, tumorectomy, or lumpectomy) with axillary lymph node dissection (in which at least six lymph nodes were isolated) for operable unilateral carcinoma of the breast (stage T1–T3). After providing written informed consent, all patients were randomly assigned to a treatment group within 8 weeks after surgery. All patients had at least one axillary lymph node that was positive for cancer on histological examination. The margins of resected specimens had to be histologically free of invasive carcinoma and ductal carcinoma in situ. A complete staging workup was carried out within 16 weeks before registration in the study. The workup included bilateral mammography, chest x-ray, abdominal ultrasonography or computed tomography, bone scan, and assessment of the left ventricular ejection fraction by use of multiple gated acquisition scanning or echocardiography. All patients were examined to ensure adequate bone marrow as well as liver and renal function (the required determinations were as follows: absolute neutrophil count of $>1.2 \times 10^9$ cells per liter, platelet count of $>100\,000 \times 10^9$

platelets per liter, hemoglobin level of >10 g/dL, total bilirubin level of ≤1× the upper limit of normality [ULN] according to each institution's guidelines, alkaline phosphatase of ≤2.5× ULN, aspartate transaminase of ≤1.5× ULN, and serum creatinine of ≤1× ULN or measured or calculated creatinine clearance of >60 mL/min). Criteria for exclusion were advanced disease (ie, stage T4, N2 or N3, or M1), a history of other cancers, motor or sensory neuropathy of grade 2 or more (according to the National Cancer Institute Common Toxicity Criteria), pregnancy, lactation, or any serious illness or medical condition other than breast cancer.

The study was approved by the institutional review boards of all participating hospitals and by the Spanish Government Health Authorities. The trial was conducted according to Good Clinical Practice and International Conference on Harmonization rules, including on-site verification of all relevant source data by GEICAM monitors. The study was registered at www.clinicaltrials.gov (identifier code = NCT00129922). The participating investigators are listed in the Appendix.

Study Design

Eligible patients were stratified according to institution, menopausal status, and number of involved axillary lymph nodes (one to three vs four or more) and randomly assigned to the control or experimental arm by means of a computer program. Treatment in the control arm consisted of six 21-day cycles of FEC (5-fluorouracil at 600 mg/m^2 body surface area, intravenous epirubicin at 90 mg/m^2, and cyclophosphamide at 600 mg/m^2, which was administered intravenously). All drugs were administered on day 1. Treatment in the experimental (FEC-P) arm consisted of four 21-day cycles of the same FEC schedule and, after 3 weeks of no treatment, eight 1-week courses of paclitaxel at 100 mg/m^2 via a 60-minute intravenous infusion.

The primary endpoint was 5-year DFS, which was defined as the time from randomization to the date of a clinical relapse (with histopathologic confirmation or radiological evidence of tumor recurrence), a second cancer (with the exception of skin cancer other than melanoma, ductal or lobular carcinoma in situ of the breast, or in situ carcinoma of the cervix), or death, whichever occurred first. The trial definition of DFS was coincident with the definition of invasive disease–free survival in the Standardized Definitions for Efficacy and End Points in Adjuvant Breast Cancer Trials (STEEP) System (14). Secondary endpoints included overall survival (defined as the time from randomization until death from any cause) and analysis of the prognostic and predictive value of the molecular markers hormonal receptor status and HER2/neu status, and safety. Although it was not prospectively planned as part of the original protocol, an analysis of distant relapse–free survival (defined as the time from randomization to the date of a distant breast cancer relapse or death from any cause) was also performed. The trial definition of distant relapse–free survival was coincident with the definition in the STEEP System.

Concomitant Therapy and Dose Modifications

All patients receiving FEC had appropriate prophylactic antiemetic treatment that included corticoids and serotonin antagonists. Before paclitaxel administration, patients received dexamethasone (10 mg), ranitidine (50 mg), and diphenhydramine (50 mg). The study protocol did not permit primary prophylaxis with granulocyte colony-stimulating factor. However, the administration of granulocyte colony-stimulating factor was mandatory among patients who had at least one episode of febrile neutropenia or an infection in subsequent cycles. Dose modifications were planned according to standard toxicity criteria. For patients with clinically relevant grade 3 toxic effects, the dose of all drugs was reduced by 25%. Treatment was to be discontinued in patients who had nonhematologic grade 4 toxic effects (according to the National Cancer Institute Common Toxicity Criteria) or who had clinically significant adverse cardiac events.

On completion of chemotherapy, tamoxifen (20 mg daily for 5 years) was mandatory for all patients whose tumors were positive (according to the institution's guidelines) for estrogen receptor, progesterone receptor, or both. In September 2005, an amendment allowing the administration of aromatase inhibitors to menopausal women was introduced to the study protocol. Radiotherapy was mandatory after breast-conserving surgery and was administered after mastectomy according to the guidelines of each participating institution, mostly to women with tumors of more than 5 cm or with four or more affected lymph nodes.

Clinical and Laboratory Evaluations

Blood counts and general biochemical and clinical assessments, including those for toxic effects, were performed on day 21 of each cycle during FEC treatment and on day 8 of every paclitaxel course. This procedure was continued every 3 months for the first 2 years of follow-up and every 6 months for the following 3 years, after which the assessments were performed annually. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 1.0. Follow-up visits were scheduled every 3 months in years 1 and 2 after chemotherapy, every 6 months in years 3–5, and yearly thereafter. Hematologic and biochemical determinations were performed at each visit. Chest radiography was repeated every 6 months for the first 5 years of follow-up, and mammography was repeated annually during follow-up.

Paraffin-embedded tumor samples, which were taken at the time of surgery, were processed centrally in the Diagnostic Molecular Pathology Laboratory at the Centro de Investigación del Cáncer (CIC)-Salamanca. Tumor tissue was analyzed in tissue microarrays containing three cores from each tumor sample, with each core being 0.6 mm in diameter. The hormone receptor status of tumors was evaluated by immunohistochemical analysis for progesterone receptor (with anti–progesterone receptor antibodies, clone PgR636, dilution 1:50, product M3569, DAKO, Carpinteria, CA) and estrogen receptor (anti–estrogen receptor antibodies, clone 1D5, dilution 1:35, product M7047, DAKO) by the use of the DAB Map system (Ventana Medical Systems, Tucson, AZ). Staining was scored according to the Allred method (15), which scores the number of immunoreactive cells (as 0–5) and the staining intensity (as 0–3) by use of a semiquantitative scale; the Allred score is the sum of both results. Allred scores of less than 3 were considered negative. Tumors were considered hormone receptor positive if they were either estrogen receptor or progesterone receptor positive. *HER2* gene amplification was evaluated by fluorescence in situ hybridization (FISH) (with the *HER2* FISH pharmDx kit, product K5331,

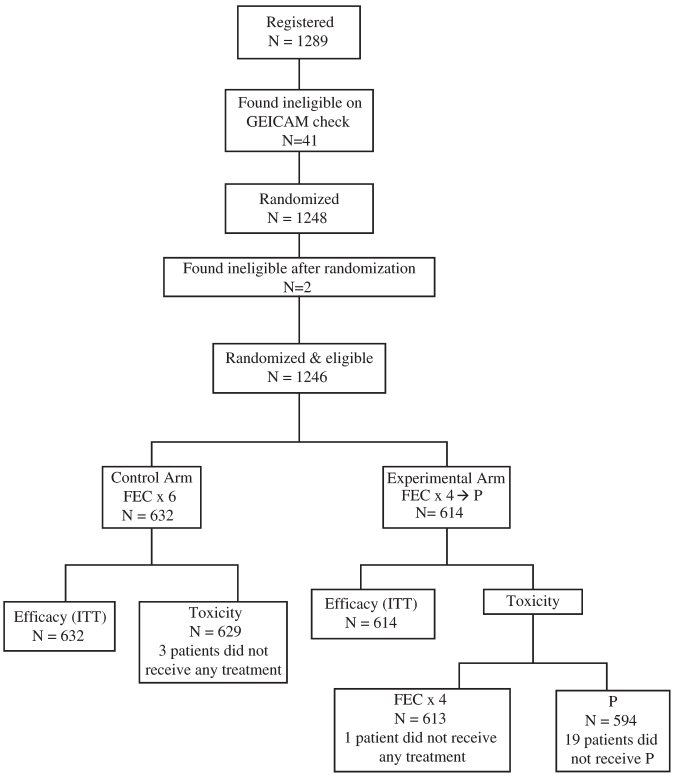

Figure 1. CONSORT trial flow diagram.

DAKO, Glostrup, Denmark), with a positive result being defined as a *HER2* gene to chromosome 17 ratio of more than 2. HER2 protein overexpression was evaluated with the DAKO HercepTest kit (product K5207, DAKO, Glostrup) by following the manufacturer's instructions. Scoring criteria for this technique include the intensity and pattern of membrane staining (ie, the whole membrane, partial staining) (16). Scoring values ranged between 0 and 3. A score of 3 was considered as a positive test. Results were independently evaluated by two pathologists at the CIC-Salamanca. Final score for each tumor sample was the mean score from three cores corresponding to each specimen. When a core was missing, the final score was assumed to correspond to the mean of all the scores available for evaluation. The maximum discrepancy in Allred scores allowed between both observers was two points, and the value used in the statistical analyses was the mean score from both individuals. No discrepancies were allowed in HER2 status results; both observers were obliged to reach a consensus.

Statistical Analyses

The primary endpoint was DFS at 5 years. When the trial was designed, the 5-year DFS was estimated as 60% for the control arm. A sample size of 1250 patients (625 in each arm) was calculated as being necessary to detect an expected 8% absolute difference in favor of the FEC-P arm. The hypothesis tests were two-sided, and the values for α and β accepted as being statistically significantly were .05 and .2, respectively. Survival variables (ie, relapse and death) were analyzed by use of the Kaplan–Meier method (17). Log-rank test was used to compare time-to-event data between both treatment arms. The Cox proportional hazards model was used to evaluate the effect on 5-year DFS of age (≤50 vs >50), menopausal status (premenopausal vs postmenopausal), tumor size (≤2.5 vs >2.5 cm), lymph node status (one to three vs four or more), and hormone receptor status according to each institution determination (positive vs negative) (intention-to-treat population). The same variables, plus the interaction of HER2 status and paclitaxel and of hormone receptor status and paclitaxel, were included in a multivariable Cox proportional hazards model analysis applied to the subset of patients whose tumor samples were centrally analyzed for HER2 and hormone receptor status. The interaction effect was defined as the ratio of hazard ratios (HRs) for recurrence in HER2-positive vs HER2-negative tumors and in hormone receptor–positive (ie, positive for estrogen and/or progesterone receptors) vs –negative (ie, negative for both estrogen and progesterone receptors) tumors. We verified that the data conformed to the assumptions for using the Cox model by a visual method with the risk function logarithm and by evaluating the log-lineal relation assumption with the Martingale residuals. The Kaplan–Meier method was used to calculate probability estimates for DFS and overall survival. The primary analysis was conducted according to the intention-to-treat principle, and a stratified log-rank test was used to compare patients in the FEC-P arm with those in the FEC arm with respect to both DFS and overall survival rates. The analysis of prognostic and predictive value for hormone receptor status and HER2 status was defined in the protocol, but no attempt was made to provide power calculations for subgroup analyses. Hazard ratios and 95% confidence intervals (CIs) were obtained from the Cox proportional hazards models. The trial data were collected and maintained by the GEICAM. All analyses were conducted according to protocol. Source verification of all relevant data was performed by GEICAM monitors. The manuscript was drafted by two of the authors (M. Martín and Á. Rodríguez-Lescure) and modified following review by all coauthors.

Results

Patients and Patient Characteristics

From November 1, 1999, through June 30, 2002, a total of 1289 women from 65 GEICAM institutions were considered potential subjects for the trial (Figure 1). The patient selection criteria were scored on a specially designed questionnaire that was sent by fax to the GEICAM staff. The staff used the questionnaires to determine eligibility for each patient; 41 patients were found to be ineligible. The remaining 1248 eligible patients were assigned to treatment with six cycles of FEC only or to treatment with four cycles of FEC followed by 8 weeks of paclitaxel treatment (FEC-P). Two patients who were initially considered eligible and randomly assigned to treatment in the trial were later found to have metastatic disease via computed tomography scans performed after registration and were censored from the trial. Therefore, 1246 patients were eligible and randomly assigned to the FEC arm (n = 632) or to the FEC-P arm (n = 614). The efficacy analysis was based on the intention-to-treat principle in eligible patients (n = 1246), regardless of treatment compliance. Tumor samples were available for 928 of these patients; data on hormone receptor status were available for 923 and on HER2 status were available for 926.

Table 1. Characteristics of the patients in the GEICAM 9906 trial and their tumors*

Characteristic	FEC arm (n = 632)	FEC-P arm (n = 614)	*P* value†
Median age (range), y	50 (24–76)	50 (23–76)	.42
Menopausal status, No. (%)			
Premenopausal	343 (54.3)	335 (54.6)	.92
Postmenopausal	289 (45.7)	279 (45.4)	
Primary tumor stage and size, No. (%)			
T1; ≤2 cm	255 (40.4)	277 (45.1)	.21
T2; 2–5 cm	342 (54.1)	302 (49.1)	
T3; >5 cm	35 (5.5)	35 (5.7)	
No. of ALN involved, No. (%)			
1, 2, or 3	392 (62.0)	386 (62.9)	.76
≥4	240 (38.0)	228 (37.1)	
Hormonal receptor status, No. (%)			
Investigator's report (n = 1242)‡			
Positive	500 (79.1)	516 (84.1)	.024
Negative	130 (20.6)	96 (15.6)	
Central determination (n = 923)§			
Positive	299 (63.6)	306 (67.5)	.21
Negative	171 (36.4)	147 (32.5)	
HER2 status‖, No. (%)			
Positive	95 (20)	93 (20.6)	.90
Negative	380 (80)	358 (79.4)	
Breast surgery, No. (%)			
Breast-conserving surgery	247 (39.1)	248 (40.4)	.64
Mastectomy	385 (60.9)	366 (59.6)	
Radiotherapy, No. (%)			
Yes	444 (70.3)	435 (70.8)	.82
No	188 (29.7)	179 (29.2)	
Histopathology grade¶, No. (%)			
GX	53 (8.4)	56 (9.1)	.78
G1	85 (13.4)	93 (15.1)	
G2	271 (42.9)	257 (41.9)	
G3	223 (35.3)	208 (33.9)	
Histological type, No. (%)			
Infiltrating ductal carcinoma	543 (85.9)	517 (84.2)	.344
Infiltrating lobular carcinoma	57 (9.0)	70 (11.4)	
Other	32 (5.1)	27 (4.4)	

* GEICAM = Grupo Español para la Investigación del Cáncer de Mama (Spanish Group for the Investigation of Breast Cancer); FEC = fluorouracil, epirubicin, and cyclophosphamide; FEC-P = FEC and paclitaxel; ALN = axillary lymph node.

† Two-sided χ^2 and two-sided *t* tests.

‡ Hormonal receptor status was not known for four patients.

§ Allred score (15).

‖ HER2 status was determined centrally for 926 patients by use of fluorescence in situ hybridization (16).

¶ Grade was determined according to Bloom–Richardson score system (18). GX = grade not known.

The characteristics of eligible patients and their tumors are shown in Table 1. In general, the two treatment arms were well balanced in terms of demographic and tumor characteristics, except for hormone receptor status; patients in the FEC-P arm had a higher percentage of hormone receptor–positive tumors than those in the control FEC arm (79.1% vs 84.1%, difference = 5%, 95% CI = 1.7% to 9.3%; *P* = .024). This imbalance, however, was not observed among the 923 patients for whom a central review of hormone receptor status was available.

Treatment

Three patients in the FEC arm and one in the FEC-P arm did not receive adjuvant therapy for the following reasons: patient refusal (one patient), loss to follow-up after randomization (one patient), and intercurrent disease (two patients). Consequently, 1242 (99.7%) of the 1296 patients started treatment as specified in the protocol (629 in the FEC arm and 613 in FEC-P arm) and were included in the safety analysis. Fourteen patients in the FEC arm received fewer than the planned six cycles of therapy. An additional patient who had been assigned to the FEC arm withdrew consent and received only four cycles of FEC followed by 8 weeks of paclitaxel. Nineteen (3%) of the 614 patients assigned to the FEC-P arm did not receive the weekly paclitaxel treatment (nine patients who refused treatment, six who experienced a toxic effect during FEC treatment, and four whose treatment was stopped at the decision of the physician when they had received only four cycles of FEC).

The median relative dose intensity of FEC was 99% in both arms. The median relative dose intensity of weekly paclitaxel in the 594 patients who received this drug was 99.5%. Radiation therapy

Table 2. Analysis of events in GEICAM 9906 trial according to the intention-to-treat principle*

Event	No. of patients (%)	
	FEC (n = 632)	FEC-P (n = 614)
No event	439 (69.5)	468 (76.2)
An event	193 (30.5)	146 (23.8)
Relapse of breast cancer	174 (27.6)	113 (18.4)
Local only, regional only, or both	30 (4.8)	11 (1.8)
Distant	141 (22.3)	101 (16.4)
Local and second primary	1 (0.2)	0 (0.0)
Unknown†	2 (0.3)	1 (0.2)
Second primary cancer	16 (2.5)	23 (3.7)
Contralateral breast cancer	4 (0.6)	7 (1.1)
Other cancer	12 (1.9)	15 (2.4)
Unknown	0 (0.0)	1 (0.2)
Death	3 (0.5)	10 (1.6)
Toxic death	1 (0.2)	4 (0.6)
Other noncancer death	2 (0.3)	6 (1.0)

* GEICAM = Grupo Español para la Investigación del Cáncer de Mama (Spanish Group for the Investigation of Breast Cancer); FEC = fluorouracil, epirubicin, and cyclophosphamide; FEC-P = FEC and paclitaxel.

† Breast cancer relapse, unknown site.

after chemotherapy was administered to 445 (70.4%) of the 632 patients in the FEC arm and 435 (70.8%) of the 614 patients in the FEC-P arm. Hormonal adjuvant therapy was administered to 491 (77.7%) patients in the FEC arm and 504 (82.1%) patients in the FEC-P arm. Tamoxifen alone (for 5 years) was administered to 258 (40.8%) patients in the FEC arm and to 256 (41.7%) in the FEC-P arm. Tamoxifen followed by aromatase inhibitors (for 5 years in total) was administered to 218 (34.5%) patients in the FEC arm and 241 (39.3%) patients in the FEC-P arm. A few patients in each arm (15 in the FEC arm and 7 in the FEC-P arm) received aromatase inhibitors alone. Thirty-four patients with hormone receptor–positive tumors (2.7%) of the 1246 patients (17 in each arm) did not receive any hormonal therapy.

Efficacy

Overall, at a median follow-up of 66 months, 339 DFS events (ie, relapse, second malignancy, or death from any cause, whatever happen first) had been registered (193 of the 632 patients in the FEC arm and 146 of the 614 patients in the FEC-P arm) (Table 2). The estimated rates of DFS at 5 years (Figure 2, A) were 78.5% in the FEC-P arm and 72.1% in the FEC arm (difference = 6.4%, 95% CI = 1.6% to 11.2%; P = .006, stratified log-rank test). Disease-free survival was better in the FEC-P arm than in the FEC arm (unadjusted HR for relapse in the FEC-P arm compared with the FEC arm = 0.74, 95% CI = 0.60 to 0.92; P = .006). After adjustment for lymph node status, age, tumor size, histology, hormone receptor status, and hormonal therapy, FEC-P treatment was found to reduce the risk of relapse by 23% compared with FEC treatment (HR of relapse = 0.77, 95% CI = 0.62 to 0.95; P = .022). The difference in DFS between the two arms was due mainly to the greater number of distant breast cancer relapses in the FEC arm than in the FEC-P arm (5-year distant relapse–free survival = 83.8% in the FEC-P arm vs 78.1% in the FEC arm; difference = 5.7%, 95% CI = 1.4% to 10.1%; HR for distant relapse = 0.70, 95% CI = 0.54 to 0.90; P = .006).

There were 168 deaths recorded (73 in the FEC-P arm and 95 in the FEC arm). Women in the FEC-P arm had a 22% lower risk of death than those in the FEC arm (adjusted HR = 0.78, 95% CI = 0.57 to 1.06; P = .110). Estimated overall survival rates at 5 years (Figure 2, C) were 89.9% in the FEC-P arm and 87.1% in the FEC arm (difference = 2.8%, 95% CI = 0% to 6.4%; P = .109).

Analysis of Subtypes

Tumor samples were available from 928 (74.5%) of the 1246 eligible patients in the trial and were assessed for HER2 amplification and hormone receptor expression at the central laboratory. The demographic and prognostic features, as well as DFS and overall survival, of patients whose tumor samples were and were not centrally tested were similar to each other (data not shown). The *HER2* gene was amplified, as assessed by FISH, in 20.3% of tumor samples. Hormone receptor expression was positive in 65.5% of samples (Allred score = 3–8). Both treatment arms had similar proportions of women with HER2-positive and hormone receptor–positive tumors.

Cox regression analysis was performed for the 928 patients from whom tumor samples were available. The dependent variable in the analysis was DFS; the independent variables were age, type of chemotherapy (FEC vs FEC-P), number of involved axillary lymph nodes, tumor size, hormone receptor status, HER2 status, HER2–paclitaxel interaction, and hormone receptor–paclitaxel interaction. Five of these independent variables were associated with DFS: type of chemotherapy (P = .017), number of involved axillary lymph nodes (P < .001), tumor size (P = .020), hormone receptor status (P = .004), and HER2 status (P = .006). Age, HER2–paclitaxel interaction, and hormone receptor–paclitaxel interaction were not statistically significantly associated with DFS.

Figure 3 shows a Kaplan–Meier analysis for DFS, in which the FEC and FEC-P arms were segregated according to hormone receptor status and HER2 status. The results remained the same when estrogen receptor status instead of hormone receptor status was used and when the Herceptest score of 3 (instead of amplification by FISH) was used as criterion for HER2 positivity (data not shown).

Toxicity

Side effects (grade 3 or 4, observed in >4% of patients) that were worse in the FEC arm than the FEC-P arm were neutropenia (25.5% vs 19.1%, respectively), febrile neutropenia (9.5% vs 5.1%), fatigue (2.4% vs 4.2%), nausea (5.9% vs 5.4%), vomiting (9.9% vs 7.3%), and stomatitis (4.9% vs 3.1%). No deaths from sepsis occurred in either arm. Amenorrhea (transient or irreversible) was reported in 58.0% of premenopausal patients in the FEC arm and 65.0% in the FEC-P arm. Grade 2 alopecia was reported in more than 90% of patients in both arms. Toxic effects observed in the FEC-P arm alone were peripheral sensory neuropathy (grade 2 = 22.2%, grade 3 = 3.7%) and arthralgia or myalgia (grade 2 = 20.6%, grade 3 = 2.8%). Peripheral neuropathy reverted in all patients after treatment concluded. Five deaths were reported by the investigators as possible toxic deaths (two from myocardial infarction during FEC treatment, one from pulmonary embolism

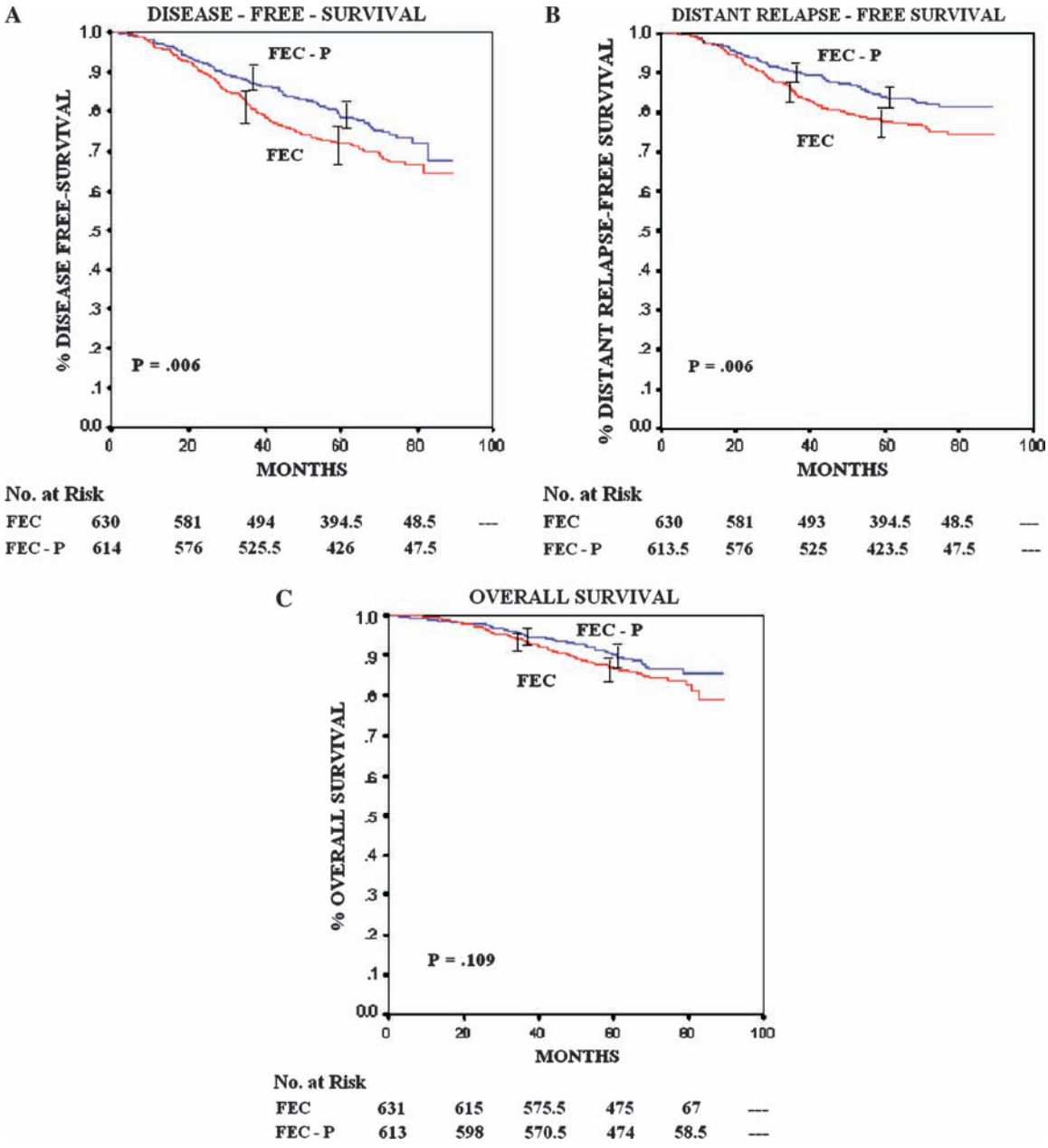

Figure 2. Kaplan–Meier analysis of survival of patients in both arms of the Grupo Español para la Investigación del Cáncer de Mama (GEICAM [Spanish Group for the Investigation of Breast Cancer]) trial 9906. All patients were analyzed on an intention-to-treat basis. **Error bars** = 95% confidence intervals. **A)** Disease-free survival. **B)** Distant relapse–free survival. **C)** Overall survival. All statistical tests were two-sided. FEC = fluorouracil, epirubicin, and cyclophosphamide; FEC-P = FEC and paclitaxel.

during FEC treatment, and two sudden deaths—one that occurred 2 months after chemotherapy and the other that occurred 4 months after chemotherapy). Grade 2 left ventricular function toxicity was reported in 7.2% of patients in the FEC arm and 7.8% of those in the FEC-P arm.

Discussion

The GEICAM 9906 trial showed that lymph node–positive breast cancer patients treated with adjuvant therapy consisting of four cycles of FEC-P had statistically significantly better 5-year DFS than those treated with six cycles of FEC (78.5% vs 72.1%, $P = .006$). This difference was due mainly to the greater number of distant breast cancer relapses in the FEC arm. At a median follow-up of 66 months, there was also better overall survival in the FEC-P arm, although the difference was not statistically significant (estimated overall survival rates at 5 years of 89.9% in the FEC-P arm and 87.1% in the FEC arm; $P = .110$.). Five-year distant relapse–free survival was statistically significantly better in the FEC-P arm than in the FEC arm (83.8% vs 78.1%; $P = .005$). Because distant relapse–free survival is usually associated with overall survival (8,9), a statistically significant benefit in overall survival may become evident with a more protracted follow-up. In fact, the small sample size of the GEICAM 9906 trial, its

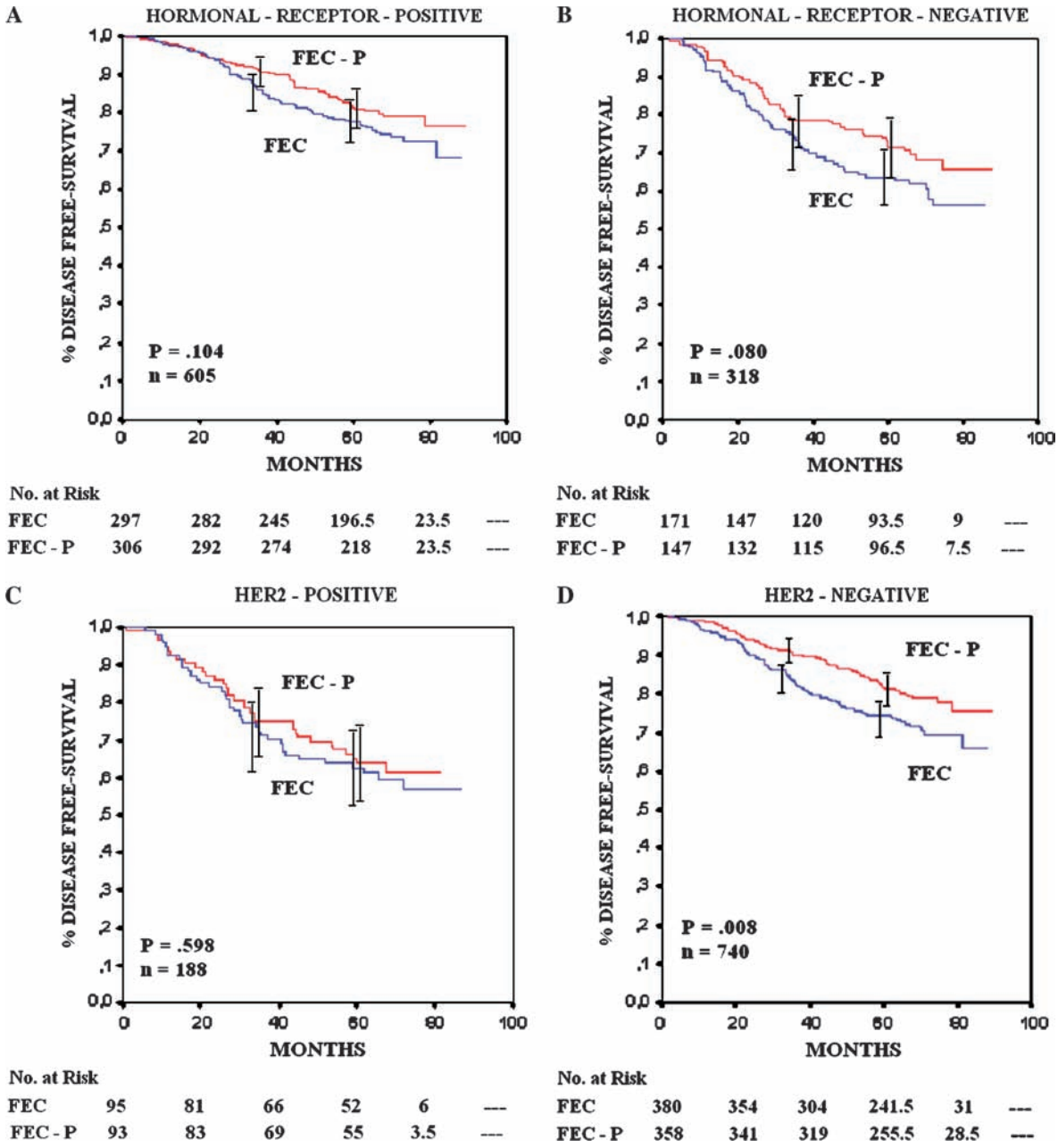

Figure 3. Kaplan–Meier analysis of disease-free survival of patients in both arms of the Grupo Español para la Investigación del Cáncer de Mama (GEICAM [Spanish Group for the Investigation of Breast Cancer]) trial 9906 according to hormone receptor status and HER2 status. **Error bars** = 95% confidence intervals. **A)** Hormone receptor–positive patients. **B)** Hormone receptor–negative patients. **C)** HER2-positive patients. **D)** HER2-negative patients. All statistical tests were two-sided. FEC = fluorouracil, epirubicin, and cyclophosphamide; FEC-P = FEC and paclitaxel.

main limitation, could explain the lack of a statistically significant difference in overall survival between arms after a median follow-up of 66 months.

The benefit obtained with the FEC-P compared with FEC (23% reduction in the risk of relapse and 22% reduction in the risk of death) in the GEICAM 9906 trial is of similar magnitude to that observed with other taxane-containing regimens (6–10), with the absolute 5-year DFS advantage in the taxane arms in these trials being in the range of 4%–7%. Because taxanes have clinically relevant side effects, identification of the population who actually benefit from these drugs is very important.

Several attempts have been made to identify the biologic characteristics of patients who benefit most from taxanes (17,19,20), but those assessments were based on retrospective subset analyses that, in most cases, precluded definitive conclusions (19–21). Hormone receptor status, one of the most important characteristics in breast tumor biology, has been proposed (19) to be a strong factor modulating the patient's response to adjuvant chemotherapy. A retrospective analysis (20) of CALGB adjuvant trials has indicated that the benefit of paclitaxel is limited mainly to estrogen receptor–negative patients. This finding, however, has not been confirmed in other taxane trials (21).

Hayes et al. (12) recently reported their results of a retrospective analysis of the interaction of HER2, paclitaxel treatment, and outcome in patients from the CALBG 9344/Intergroup 0148 trial, which compared treatment with doxorubicin and cyclophosphamide with treatment with doxorubicin and cyclophosphamide followed by paclitaxel. The study had a double randomization process, initially to three different doses of doxorubicin (60, 75, or 90 mg/m^2) and then to paclitaxel vs no paclitaxel. The authors hypothesized that HER2 status might predict greater benefit from higher doses of doxorubicin and from additional paclitaxel. Their results indicated, however, that there was no interaction between doxorubicin dose and HER2 status. Conversely, HER2 positivity, regardless of estrogen receptor status, was associated with a statistically significant benefit from paclitaxel treatment (HR for recurrence = 0.59, P = .01). The interaction between HER2 status and paclitaxel efficacy observed in the CALGB 9344/Intergroup 0148 trial has not been confirmed by the GEICAM 9906 trial. That is, we did not find a statistically significant interaction between treatment with paclitaxel and HER2 status as determined by FISH or between treatment with paclitaxel and hormone receptor status.

The difference between the GEICAM 9906 trial and the CALGB trial could be due to several factors. Although the interaction of paclitaxel treatment and HER2 status that was observed in the CALGB 9344/Intergroup 0148 trial could be due to the activity of paclitaxel itself, the outcomes could be explained by other factors as well (eg, a more appropriate chemotherapy duration in the experimental arm or an insufficient anthracycline treatment in the control arm). The design of the CALGB 9344/Intergroup 0148 trial contains two weaknesses. First, the duration of treatment was not equivalent for the paclitaxel and no-paclitaxel arms (four cycles in one and eight cycles in the other). Thus, the benefit observed could have been due merely to a more protracted chemotherapy regimen rather than to a taxane-specific effect. Duration of adjuvant chemotherapy itself can be a determinant of outcome, as shown in a randomized trial by the French Adjuvant Study Group (22) that demonstrated that a regimen of six cycles of FEC with epirubicin at 50 mg/m^2 was superior to a regimen of three cycles of FEC with epirubicin at 75 mg/m^2 or FEC with epirubicin at 50 mg/m^2. Second, the regimen in the control arm (ie, four cycles of doxorubicin and cyclophosphamide) could be a suboptimal adjuvant treatment regimen (23,24), particularly in patients whose tumors overexpress HER2 (5). In individual trials, CMF treatment and doxorubicin and cyclophosphamide treatment were equivalent in terms of DFS and overall survival (25), whereas FEC regimens (26,27) and cyclophosphamide, doxorubicin, and fluorouracil regimens (28) were superior to CMF. Because HER2-positive patients obtain the maximum benefit with anthracyclines (5), the administration of an appropriate anthracycline regimen to this particular subset of patients appears to be of critical importance.

The design of the GEICAM 9906 trial was intended to avoid some of the weaknesses of the CALBG 9344/Intergroup 0148 trial. The duration of chemotherapy was similar in both arms of GEICAM 9906. The control FEC arm had six cycles of chemotherapy with the standard dose of cyclophosphamide (600 mg/m^2) and an appropriate dose of epirubicin (90 mg/m^2) and 5-fluorouracil (600 mg/m^2). In the experimental FEC-P arm, weekly paclitaxel also administered at the maximum tolerated doses was selected to deliver the maximum dose intensity of the drug over a relatively short period of time.

Finally, the differences in subset results between the GEICAM 9906 trial and the CALBG 9344/Intergroup 0148 trial could be due to the retrospective, and unplanned, nature of the analyses. Unfortunately, none of these first-generation adjuvant taxane trials had been designed to determine the effectiveness of taxanes in subgroups of patients with different tumor biomarkers. Retrospective identifications (by means of multiple comparisons) of the subgroups of patients who would really benefit from taxanes can lead to spurious treatment associations (false-positive results); on the other hand, the post hoc subdivision of data into subgroups reduces the study's power to detect statistically significant treatment differences (leading to possible false-negative results).

Unfortunately, because the benefit of taxanes has been established in the overall population of patients with early breast cancer, new prospective studies evaluating combination treatments with and without taxanes in patients with specific subtypes of breast cancer (ie, hormone receptor–positive disease) cannot be conducted because of ethical concerns of a no-taxane treatment arm. Hence, retrospective analyses are likely to be the only source of information on this subject.

References

1. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomized trials. *Lancet.* 1998; 352(8785):930–942.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. *Lancet.* 2005;365(9132):1687–1717.
3. Jensen BV. Cardioconsequences of anthracycline-containing therapy in patients with breast cancer. *Semin Oncol.* 2006;33(suppl 8):S15–S21.
4. Knoop AS, Knudsen H, Baslev B, et al. Retrospective analysis of topoisomerase IIa amplifications and deletions as predictive markers in primary breast cancer patients randomly assigned to cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide, epirubicin, and fluorouracil: Danish Breast cancer Cooperative Group. *J Clin Oncol.* 2005;23(30): 7483–7490.
5. Pritchard KI, Shepherd LE, O´Malley FP, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med.* 2006;354(20): 2103–2111.
6. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol.* 2003;21(6):976–983.
7. Mamounas EP, Bryant J, Lembersky BC, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP-B 28. *J Clin Oncol.* 2005;23(16): 3686–3696.
8. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med.* 2005;352(22):2302–2313.
9. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PASC 01 trial. *J Clin Oncol.* 2006;24(36):5664–5671.
10. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol.* 2006;24(34): 5381–5387.
11. Martin M. Molecular biology of breast cancer. *Clin Transl Oncol.* 2006; 8(6):7–14.

12. Hayes DF, Thor AD, Dressler LG, et al. HER2 and response to paclitaxel in node-positive breast cancer. *N Engl J Med.* 2007;357(15):1496–1506.
13. Martin M, Rodriguez-Lescure A, Ruiz A, et al. Multicenter, randomized phase III study of adjuvant chemotherapy for node positive breast cáncer comparing 6 cycles of $FE_{90}C$ versus 4 cycles of $FE_{90}C$ followed by 8 weekly paclitaxel administrations: interim efficacy analysis of GEICAM 9906 trial. *Breast Cancer Res Treat.* 2005;94(suppl 1):S20.
14. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol.* 2007;25(15):2127–2132.
15. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol.* 1998;11(2):155–168.
16. Jacobs TW, Gown AM, Yaziji H, et al. Specificity of HercepTest in determining Her-2/neu status of breast cancer using the United States Food and Drug Administration-approved scoring system. *J Clin Oncol.* 1999; 17(7):1983–1987.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53(5):457–481.
18. Bloom HJG, Richardson WW. Histological grading and prognosis in breast cancer. *Br J Cancer.* 1957;11(8):359–377.
19. Albain K, Barlow W, O´Malley F, et al. Concurrent (CAFT) versus sequential (CAF-T) chemohormonal therapy (cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen) versus T alone for postmenopausal, node-positive, oestrogen and/or progesterone receptor-positive breast cancer; mature outcomes an new biological correlates on phase III intergroup trial 0100 (SWOG-8814). *Breast Cancer Res Treat.* 2004;88(suppl 1):abstract 37.
20. Berry DA, Cirrincione C, Craig Henderson I, et al. Oestrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. *JAMA.* 2006;295(14):1658–1667.
21. Martin M, Mackey J, Vogel C. Benefit from adjuvant taxanes and endocrine responsiveness in breast cancer. *Breast.* 2007;16(S2):S127–S131.
22. Fumoleau P, Kerbrat P, Romestaing P, et al. Randomized trial comparing six versus three cycles of epirubicin-based adjuvant chemotherapy in premenopausal, node-positive breast cancer patients: 10-year follow-up results of the French Adjuvant Study Group 01 trial. *J Clin Oncol.* 2003;21(2):298–305.
23. Trudeau M, Charbonneau F, Gelman K, et al. Selection of adjuvant chemotherapy for treatment of node-positive breast cancer. *Lancet Oncol.* 2005;6(11):886–898.
24. Levine MN, Eisen A. Anthracycline adjuvant chemotherapy: how much is enough? *J Clin Oncol.* 2001;19(3):599–601.
25. Fisher B, Brown A, Dimitrov N, et al. Two months of doxorubicin-cyclophosphamide with and without interval re-induction therapy compared with 6 months of cyclophosphamide, methotrexate and fluorouracil in positive-node breast cancer patients with tamoxifen-non-responsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol.* 1990;8(9):1483–1496.
26. Levine MN, Bramwell VH, Pritchard KI, et al. Randomized trial of intensive cyclophosphamide, epirubicin and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate and fluorouracil in premenopausal women with node-positive breast cancer. *J Clin Oncol.* 1998;16(8):2651–2658.
27. Mouridsen H, Andersen J, Andersson M, et al. Adjuvant anthracycline in breast cancer: improved outcome in premenopausal patients following substitution of methotrexate in the CMF combination with epirubicin. *Proc Am Soc Clin Oncol.* 1999;18:68.
28. Martin M, Villar A, Solé-Calvo A, et al. Doxorubicin in combination with fluorouracil and cyclophosphamide (i.v. FAC regimen, day 1, 21) versus methotrexate in combination with fluorouracil and cyclophosphamide (i.v. CMF regimen, day 1, 21) as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. *Ann Oncol.* 2003;14(6): 833–842.

Notes

The first two authors (M. Martín and Á. Rodríguez-Lescure) contributed equally to this study.

Bristol-Myers Squibb and Pharmacia provided unrestricted grants for the conduct of the trial. The authors thank Edith A. Perez (Mayo Clinic, Jacksonville, FL) for reviewing the original manuscript and Maribel Casas and María José Escudero for the statistical analyses. Editorial assistance was by Dr Peter R. Turner of t-SciMed (Reus, Spain).

Dr M. Martín is a consultant for Bristol Myers Squibb and for Sanofi-Aventis. Dr E. de Alava is currently conducting research that is sponsored by Novartix and PharmaMar among subjects who do not have breast cancer.

The authors had full responsibility in the design of the trial, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

Manuscript received December 26, 2007; revised March 25, 2008; accepted April 10, 2008.

Appendix

The following investigators, with their affiliations, participated in the GEICAM 9906 trial:

Hospital Universitario San Carlos, Madrid, Spain—M. Martín and J. A. López García-Asenjo; Hospital Universitario de Elche, Elche, Spain—Á. Rodríguez-Lescure; Instituto Valenciano de Oncología, Valencia, Spain—A. Ruiz and S. Almenar; Hospital Virgen de la Victoria, Málaga, Spain—E. Alba and Luis Vicioso; Complejo Hospitalario Juan Canalejo, La Coruña, Spain—L. Calvo and Mª Dolores Guitián; Hospital Vírgen del Rocío, Sevilla, Spain—M. Ruiz-Borrego and J. Palacios; Hospital La Fe, Valencia, Spain—B. Munárriz and F. Vera; Hospital Universitario de Salamanca, Salamanca, Spain—C. A. Rodríguez; Hospital Ramón y Cajal, Madrid, Spain—C. Crespo and J. Fernando González-Palacios; Centro Oncológico de Galicia, La Coruña, Spain—M. Ramos and Alberto de la Cruz; Hospital De Cabueñes, Gijón, Spain—J. M. Gracia Marco and Jesús Martín Angulo; Hospital Clínico de Valencia, Valencia, Spain—A. Lluch and Jauma Ferrer; Hospital Donostia, San Sebastián, Spain—I. Álvarez and Irune Ruiz; Hospital Parc Taulí, Sabadell, Spain—M. Á. Seguí and Amparo Sáez; Hospital Clínico Lozano Blesa, Zaragoza, Spain—J. I. Mayordomo and Manuel Moros; Hospital Miguel Server, Zaragoza, Spain—A. Antón and M. José Ríos; Complejo Hospitalario Puerta del Mar, Cádiz, Spain—J. M. Baena and M. Jesús Palomo; Instituto Oncológico de Guipúzcoa, San Sebastián, Spain—A. Plazaola and Ricardo Rezola; Clínica Corachan, Barcelona, Spain—A. Modolell and Pilar De las Heras; Hospital Universitario San Joan de Reus, Reus, Spain—A. Pelegrí and Francisco Riu; Complejo Hospitalario Xeral Calde, Lugo, Spain—J. R. Mel and Jesús Alba; Hospital Provincial de Córdoba, Córdoba, Spain—E. Aranda and Elena Fuentes; Hospital General de Alicante, Alicante, Spain—E. Adrover and Gloria Peiró; Hospital Provincial de Zamora, Zamora, Spain—J. V. Álvarez; Hospital San Cecilio de Granada, Granada, Spain—J. L. G. Puche and José Aneiros; Hospital Ciudad de Jaén, Jaén, Spain—P. Sánchez-Rovira and Cristóbal Cueva; Hospital Mutua de Terrasa, Terrasa, Spain—Sonia Gonzalez; Hospital Marqués de Valdecilla, Santander, Spain—J. M. López-Vega and M. Francisca Garijo.