

ORIGINAL ARTICLE

Adjuvant Docetaxel or Vinorelbine with or without Trastuzumab for Breast Cancer

Heikki Joensuu, M.D., Pirkko-Liisa Kellokumpu-Lehtinen, M.D., Petri Bono, M.D., Tuomo Alanko, M.D., Vesa Kataja, M.D., Raija Asola, M.D., Tapio Utriainen, M.D., Riitta Kokko, M.D., Akseli Hemminki, M.D., Maija Tarkkanen, M.D., Taina Turpeenniemi-Hujanen, M.D., Sirkku Jyrkkiö, M.D., Martti Flander, M.D., Leena Helle, M.D., Seija Ingalsuo, M.D., Kaisu Johansson, M.D., Anna-Stina Jääskeläinen, M.D., Marjo Pajunen, M.D., Mervi Rauhala, M.D., Jaana Kaleva-Kerola, M.D., Tapio Salminen, M.D., Mika Leinonen, M.Sci., Inkeri Elomaa, M.D., and Jorma Isola, M.D., for the FinHer Study Investigators*

ABSTRACT

BACKGROUND

We compared docetaxel with vinorelbine for the adjuvant treatment of early breast cancer. Women with tumors that overexpressed *HER2/neu* were also assigned to receive concomitant treatment with trastuzumab or no such treatment.

METHODS

We randomly assigned 1010 women with axillary-node-positive or high-risk node-negative cancer to receive three cycles of docetaxel or vinorelbine, followed by (in both groups) three cycles of fluorouracil, epirubicin, and cyclophosphamide. The 232 women whose tumors had an amplified *HER2/neu* gene were further assigned to receive or not to receive nine weekly trastuzumab infusions. The primary end point was recurrence-free survival.

RESULTS

Recurrence-free survival at three years was better with docetaxel than with vinorelbine (91 percent vs. 86 percent; hazard ratio for recurrence or death, 0.58; 95 percent confidence interval, 0.40 to 0.85; $P=0.005$), but overall survival did not differ between the groups ($P=0.15$). Within the subgroup of patients who had *HER2/neu*-positive cancer, those who received trastuzumab had better three-year recurrence-free survival than those who did not receive the antibody (89 percent vs. 78 percent; hazard ratio for recurrence or death, 0.42; 95 percent confidence interval, 0.21 to 0.83; $P=0.01$). Docetaxel was associated with more adverse effects than was vinorelbine. Trastuzumab was not associated with decreased left ventricular ejection fraction or cardiac failure.

CONCLUSIONS

Adjuvant treatment with docetaxel, as compared with vinorelbine, improves recurrence-free survival in women with early breast cancer. A short course of trastuzumab administered concomitantly with docetaxel or vinorelbine is effective in women with breast cancer who have an amplified *HER2/neu* gene. (International Standard Randomised Controlled Trial number, ISRCTN76560285.)

From the Department of Oncology, Helsinki University Central Hospital, Helsinki (H.J., P.B., T.A., T.U., A.H., M.T., A.-S.J., I.E.); the Department of Oncology, Tampere University Hospital (P.-L.K.-L., T.S.), and the Laboratory of Cancer Biology, Institute of Medical Technology, University of Tampere and Tampere University Hospital (J.I.), Tampere; the Department of Oncology, Kuopio University Hospital, Kuopio (V.K.); Satakunta Central Hospital, Pori (R.A.); Hämeenlinna Central Hospital, Hämeenlinna (R.K.); the Department of Oncology and Radiotherapy, Oulu University Hospital, Oulu (T.T.-H.); the Department of Oncology, Turku University Central Hospital, Turku (S.J.); South Karelia Central Hospital, Lappeenranta (M.F.); Kotka Central Hospital, Kotka (L.H.); Vaasa Central Hospital, Vaasa (S.I.); Kokkola Central Hospital, Kokkola (K.J.); Jyväskylä Central Hospital, Jyväskylä (M.P.); Kajaani Central Hospital, Kajaani (M.R.); Kemi Central Hospital, Kemi (J.K.-K.); and 4Pharma, Turku (M.L.) — all in Finland. Address reprint requests to Dr. Joensuu at the Department of Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, P.O.B. 180, FIN-00029 Helsinki, Finland.

*Other FinHer (Finland Herceptin) Study investigators are listed in the Appendix.

N Engl J Med 2006;354:809-20.

Copyright © 2006 Massachusetts Medical Society.

ADJUVANT (POSTOPERATIVE) TREATMENT has markedly reduced rates of death due to breast cancer.^{1,2} However, in 15 to 25 percent of breast carcinomas, there is amplification of the *HER2/neu* (*ErbB2*) gene, an excess of the HER2 protein in the cancer cells,³ and a high risk of recurrence.⁴⁻⁶

Trastuzumab (Herceptin, Roche) is a humanized monoclonal antibody against the HER2 protein. When administered with chemotherapy, it improves survival in advanced HER2-positive breast cancer.^{7,8} When given concomitantly with paclitaxel or after chemotherapy for 12 months as adjuvant treatment for early HER2-positive breast cancer, trastuzumab reduces the risk of recurrence by approximately 50 percent and the risk of death by approximately 30 percent.^{9,10} In these studies, the principal adverse event attributable to trastuzumab was heart failure, which occurred in 1.7 to 4.1 percent of women treated with the antibody; approximately 10 percent of trastuzumab-treated participants had a substantial decrease in the left ventricular ejection fraction. The risk of cardiac dysfunction with trastuzumab treatment increases with the use of anthracyclines.^{7,11} The long-term outcome of trastuzumab-related heart failure is unknown, although symptoms usually subside with cessation of treatment with trastuzumab and management of the condition.¹⁰

Combining trastuzumab with docetaxel, vinorelbine, cisplatin, carboplatin, or paclitaxel has resulted in the highest pooled response rates to date in the treatment of breast cancer.¹² Data obtained in vitro suggest that such combinations kill breast cancer cells by synergistic effects.^{13,14} In the FinHer (Finland Herceptin) study, we compared docetaxel with vinorelbine, administered with or without trastuzumab, as adjuvant treatment for early breast cancer. In this study, trastuzumab was administered before other cardiotoxic therapies and concomitantly with potentially synergistic chemotherapy for only nine weeks to test the hypothesis that such a schedule would limit cardiotoxicity and maintain efficacy.

METHODS

STUDY POPULATION

Women eligible for the study were less than 66 years of age, had a World Health Organization performance status of 0 or 1, and had undergone breast surgery with axillary-node dissection or

sentinel-node biopsy for invasive breast carcinoma. We required determination of steroid hormone-receptor status and HER2 expression by immunohistochemistry, according to the guidelines of each institution. When HER2 expression was scored 2+ or 3+ (on a scale of 0, 1+, 2+, or 3+), the number of copies of the *HER2/neu* gene was determined by means of chromogenic in situ hybridization in one of two reference laboratories.¹⁵

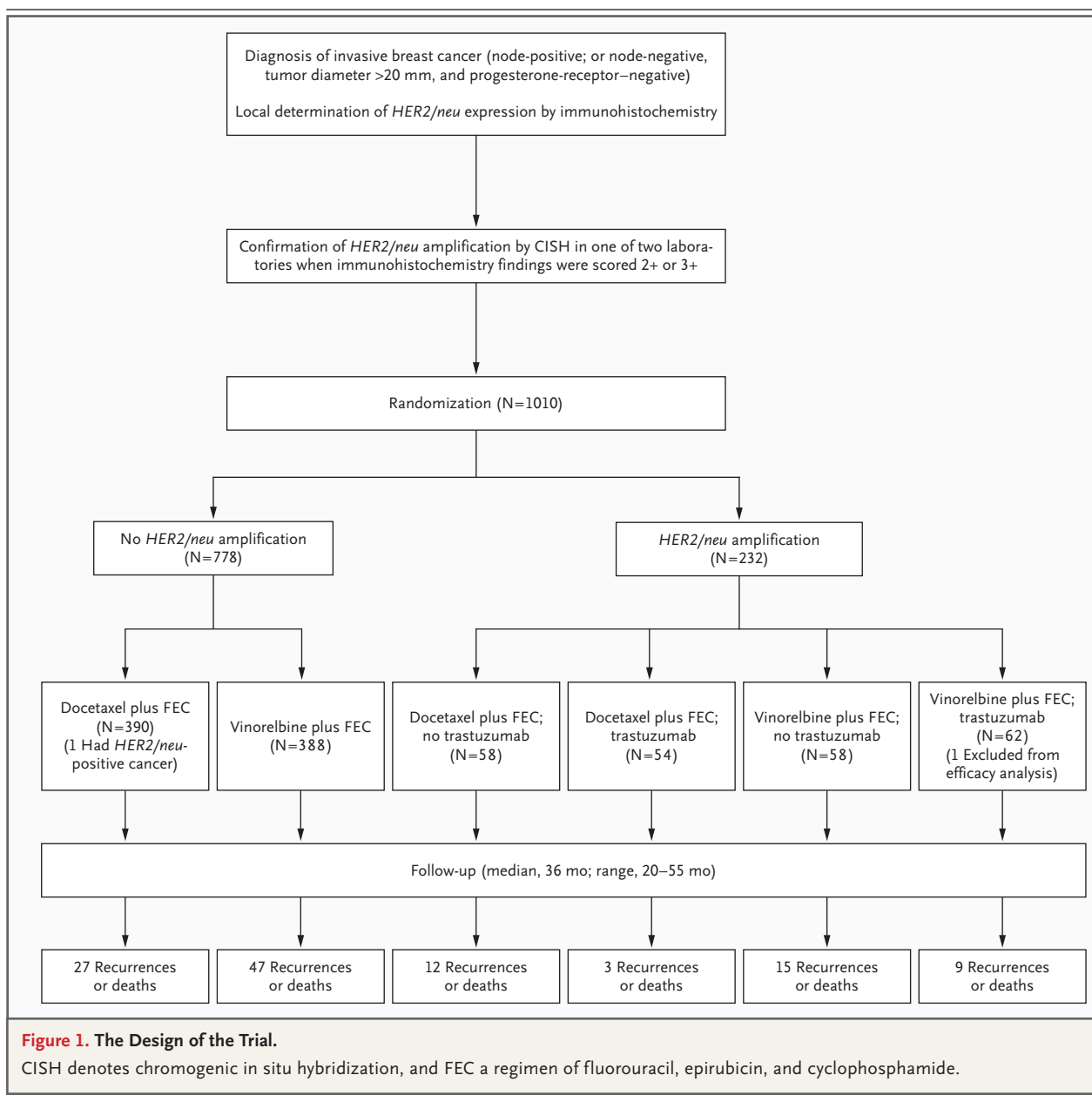
Participants were randomly assigned (centrally and with computer-assisted blinding) to a study group within 12 weeks after surgery. Eligible patients had either at least one positive axillary node (regardless of the primary tumor size or its hormone-receptor expression) or a node-negative breast-cancer mass at least 20 mm in diameter and a negative test for progesterone receptors (usually defined as staining of <10 percent of the cancer cells). The staging workup included isotope bone scanning; chest radiography or computed tomography (CT); and CT or ultrasonography of the upper abdomen.

Criteria for exclusion were distant metastases, pregnancy, severe hypertension, and cardiac disease (including cardiac failure of any degree, arrhythmia requiring regular medication, and myocardial infarction within the previous 12 months). Patients were ineligible if they had a serum bilirubin level above the upper limit of normal, an alanine or aspartate aminotransferase level greater than 1.5 times the upper limit of normal, an alkaline phosphatase level above 2.5 times the upper limit of normal, a blood leukocyte count below 3.0×10^9 per milliliter, a neutrophil count below 1.5×10^9 per milliliter, or a platelet count below 120×10^9 per milliliter.

An ethics committee at Helsinki University Central Hospital approved the study. Study participants provided written informed consent.

STUDY DESIGN

Figure 1 shows the design of the trial. Randomization was stratified according to HER2 status (positive vs. negative) and institution in this phase 3, open-label, multicenter trial. Permuted blocks were used to randomly assign all participants to receive three cycles of either docetaxel or vinorelbine. Docetaxel (Taxotere, Sanofi-Aventis) was given at a dose of 100 mg per square meter of body-surface area as a one-hour intravenous infusion on day 1 of each 21-day cycle. Vinorelbine (Navelbine, Pierre Fabre) was administered at a



dose of 25 mg per square meter as a 5-to-10-minute intravenous infusion on days 1, 8, and 15 of the 21-day cycles. After the completion of docetaxel or vinorelbine treatment, three cycles of a regimen consisting of intravenous fluorouracil at a dose of 600 mg per square meter, epirubicin at a dose of 60 mg per square meter, and cyclophosphamide at a dose of 600 mg per square meter, each administered on day 1 of a 21-day cycle (FEC), were given. The vinorelbine infusion on day 15 was omitted from the third cycle to allow the

initiation of FEC at a full dose without delay. The duration of the chemotherapy regimen was 18 weeks.

Women who had verified HER2-positive cancer were randomly assigned to receive or not to receive trastuzumab. Nine trastuzumab infusions were administered at one-week intervals; the first infusion was given on day 1 of the first docetaxel or vinorelbine cycle. The first dose was 4 mg per kilogram of body weight and the subsequent doses 2 mg per kilogram, administered over pe-

riods of 90 and 30 minutes, respectively. Trastuzumab was infused before docetaxel or vinorelbine. No trastuzumab was given during FEC administration.

The primary end point was recurrence-free survival, defined as the time from the date of randomization to the date of detection (with histologic or cytologic confirmation or with radiologic evidence) of local, distant, or contralateral invasive breast cancer or death, whichever occurred first. Secondary end points included adverse effects, the effect of treatment on the left ventricular ejection fraction, the time to distant recurrence, and overall survival, defined as time from randomization to death from any cause.

STUDY PROCEDURES

Concomitant Therapy

Patients assigned to docetaxel received six 7.5-mg doses of dexamethasone; the first two were given 12 hours and 1 hour before docetaxel infusion and the rest at 12-hour intervals after infusion. Use of prophylactic antibiotics or granulocyte colony-stimulating factors was not recommended unless one or more episodes of febrile neutropenia or severe infection occurred.

Radiotherapy was given after the completion of chemotherapy according to each institution's guidelines, but it was required after breast-conserving surgery. Tamoxifen at a dose of 20 mg per day was administered to patients with estrogen-receptor-positive or progesterone-receptor-positive tumors; this treatment was to be continued for five years.

Dose Modifications

Chemotherapy doses were reduced by 20 percent in cases of persistent hematologic toxic effects or grade 3 or 4 nonhematologic toxic effects, defined according to the National Cancer Institute Common Toxicity Criteria (version 2.0). When either docetaxel or vinorelbine was discontinued because of adverse effects, the cycles not given were replaced by an equal number of cycles of FEC. Trastuzumab was administered at full doses regardless of blood-cell counts, but infusions were deferred whenever vinorelbine or docetaxel infusions were postponed because of adverse effects.

Evaluations

Adverse effects of therapy were recorded on proto-

col-specified forms on day 21 of each chemotherapy cycle and 12 and 36 months after chemotherapy. Patients were scheduled for follow-up for a minimum of five years. Mammography was performed at one-to-two-year intervals, but otherwise follow-up was carried out according to each institution's guidelines. In the group of patients assigned to trastuzumab treatment, the left ventricular ejection fraction was measured by either echocardiography or isotope cardiography before chemotherapy, after the last FEC cycle, and 12 and 36 months after chemotherapy.

STATISTICAL ANALYSIS

The study was designed to have a power of 0.80 to detect an increase in five-year recurrence-free survival from 70 percent to 80 percent in the docetaxel-plus-FEC group as compared with the vinorelbine-plus-FEC group (with use of a two-sided test at a significance level of 0.05); approximately 150 events were required for this purpose. We estimated that 30 percent of the participants would have breast cancer with *HER2/neu* amplification and that the study would be able to detect a difference in their five-year recurrence-free survival of 50 percent to 67 percent at a power of 0.80 when approximately 1000 patients were enrolled.

Protocol-defined safety analyses took place in March 2001, September 2001, and December 2002.¹⁶ The current protocol specified that safety and early efficacy analyses were to be carried out when the median follow-up time exceeded three years; this point was reached in May 2005. The final analyses will be performed when 150 events have occurred or the median follow-up time exceeds five years. For the primary variable, a P value of less than 0.029 was considered to indicate significance, in order to maintain an overall type 1 error of 0.05 for the interim and final analysis.¹⁷

Frequency tables were analyzed with use of the chi-square test. Survival between groups was compared with use of the Kaplan-Meier life-table method and the Cox proportional-hazards model; the log-rank test was used to confirm the robustness of the analysis. Efficacy analyses were based on the intention-to-treat principle. The effects of treatment, time, the method of assessment, and their interactions with the left ventricular ejection fraction were analyzed in a repeated-measures analysis of covariance (ANCOVA) model; pretreat-

ment measurement of the ejection fraction was used as a covariate and the ejection fractions measured later as response variables. All P values are two-sided and were not adjusted for multiple testing.

Dr. Joensuu drafted the study design. The investigators initiated the study, and collected, analyzed, and maintained the data. The sponsor (the Finnish Breast Cancer Group) received grants from Sanofi-Aventis, Pierre Fabre, and Pharmacia; Roche supported the *HER2/neu* analyses. Trastuzumab was purchased from funds provided in the state budget of Finland; other study drugs were purchased by the participating institutions. The manuscript was drafted by Dr. Joensuu and modified by the coauthors. The authors determined the content of the manuscript and vouch for its accuracy and completeness.

RESULTS

PATIENTS

From October 2000 to September 2003, 1010 women (approximately 40 percent of the eligible women in Finland who received a diagnosis of breast cancer within this period, according to the Finnish Cancer Registry and other sources [www.cancer.fi])¹⁸ were randomly assigned to receive either docetaxel (502 women) or vinorelbine (508). Of these 1010 women, 232 who had an amplified *HER2/neu* gene were further randomly assigned to receive trastuzumab (116 women) or not to receive it (116). The median follow-up times were 36 and 35 months in the docetaxel and vinorelbine groups, respectively, and 37 and 35 months in the trastuzumab and no-trastuzumab (control) groups, respectively, at the time of analysis (May 19, 2005). No patient was lost to follow-up. Two women who did not receive the study treatments because of abnormal results on liver-function tests were excluded from the safety analyses, and one woman (who had been assigned to the vinorelbine group and had *HER2/neu*-positive cancer) with overt distant metastases at randomization was excluded from the survival analyses. One woman with *HER2/neu* amplification did not participate in randomization with respect to trastuzumab, and seven women were ineligible. The baseline characteristics of the groups were balanced, except that larger tumors were more common in the docetaxel group than in the vinorel-

bine group and axillary nodal metastases tended to be more frequent in the trastuzumab group than in the group that did not receive the antibody (Table 1).

Most (84.3 percent) of the cancers with strong (3+) *HER2*-protein expression on immunohistochemical analysis contained amplified *HER2/neu*. Of the cancers that stained moderately positively (2+), 26.2 percent contained amplified *HER2/neu*.

TREATMENT

In February 2002, an independent study-monitoring committee recommended that the dose of docetaxel be reduced because 36.9 percent of the women treated with this agent had received a diagnosis of neutropenic fever. Therefore, 206 of the 502 patients treated with docetaxel (41.0 percent) received 100 mg per square meter and 296 (59.0 percent) received 80 mg per square meter as the starting dose. Three docetaxel cycles were completed by 472 patients (94.0 percent), and three vinorelbine cycles were completed by 483 patients (95.1 percent). Docetaxel (100 mg per square meter), docetaxel (80 mg per square meter), and vinorelbine were given at the protocol-specified dose in 64.7, 83.9, and 82.4 percent of cycles, respectively. The most common reasons for a reduction in the dose of docetaxel were neutropenia and neutropenic infections, and the most common reason for a reduction in the dose of vinorelbine was neutropenia. The full dose of trastuzumab was administered in 99.1 percent of cycles, and 93.6 and 96.6 percent of the protocol-specified trastuzumab infusions were delivered to women in the docetaxel and vinorelbine groups, respectively.

Three or more FEC cycles were administered to 98.6 and 98.0 percent of the women assigned to docetaxel and vinorelbine, respectively, and 91.2 and 93.1 percent received FEC at the protocol-specified dose. Adjuvant radiotherapy was given to 97.0 and 97.6 percent of the patients, respectively, and tamoxifen to 71.1 and 73.8 percent.

Within the subgroup of women with *HER2/neu*-positive cancer, 54 of the women assigned to receive trastuzumab (46.6 percent) and 58 of those who did not receive trastuzumab (50.0 percent) were in the docetaxel group ($P=0.60$). The protocol-specified 100-mg dose of docetaxel was administered in 61.1 percent and 64.4 percent of the cycles in the trastuzumab and control groups,

Table 1. Characteristics of the Patients and the Tumors at Baseline.*

Variable	All Participants			Participants with <i>HER2/neu</i> + Disease		
	Docetaxel (N=502)	Vinorelbine (N=508)	P Value	Trastuzumab (N=116)	No Trastuzumab (N=116)	P Value
WHO performance status — no. (%)			0.57			0.64
0	455 (91)	455 (90)		105 (91)	107 (92)	
1	47 (9)	53 (10)		11 (9)	9 (8)	
No. of metastatic axillary nodes — no. (%)			0.73			0.06
0	57 (11)	54 (11)		12 (10)	25 (22)	
1–3	300 (60)	316 (62)		64 (55)	58 (50)	
>3	145 (29)	138 (27)		40 (34)	33 (28)	
Diameter of primary tumor — no. (%)			0.02			0.24
≤10 mm	30 (6)	52 (10)		8 (7)	8 (7)	
11–20 mm	174 (35)	185 (36)		38 (33)	27 (23)	
>20 mm	296 (59)	269 (53)		69 (59)	81 (70)	
Not available	2 (<1)	2 (<1)		1 (1)	0	
Histologic type — no. (%)			0.96†			0.51†
Ductal	390 (78)	398 (78)		106 (91)	103 (89)	
Lobular	99 (20)	98 (19)		10 (9)	11 (9)	
Other	13 (3)	12 (2)		0 (0)	2 (2)	
Histologic grade — no. (%)			0.39‡			0.51‡
1	76 (15)	74 (15)		2 (2)	3 (3)	
2	186 (37)	211 (42)		39 (34)	33 (28)	
3	214 (43)	201 (40)		73 (63)	77 (66)	
Not available	26 (5)	22 (4)		2 (2)	3 (3)	
Estrogen-receptor status — no. (%)			0.50			0.36
Positive	358 (71)	372 (73)		58 (50)	51 (44)	
Negative	144 (29)	136 (27)		58 (50)	65 (56)	
Progesterone-receptor status — no. (%)			0.35			0.13
Positive	283 (56)	301 (59)		45 (39)	34 (29)	
Negative	219 (44)	207 (41)		71 (61)	82 (71)	
<i>HER2/neu</i> amplification — no. (%)			0.67			1.00
Absent	389 (77)	388 (76)		0	0	
Present	113 (23)§	120 (24)		116 (100)	116 (100)	
Age — yr						
Median	50.8	51.0	0.72	51.4	49.9	0.19
Range	25.5–65.7	26.9–65.8		25.5–65.8	27.3–64.5	

* Percentages may not total 100, because of rounding. WHO denotes World Health Organization.

† The P value is for the ductal type as compared with the lobular and other types.

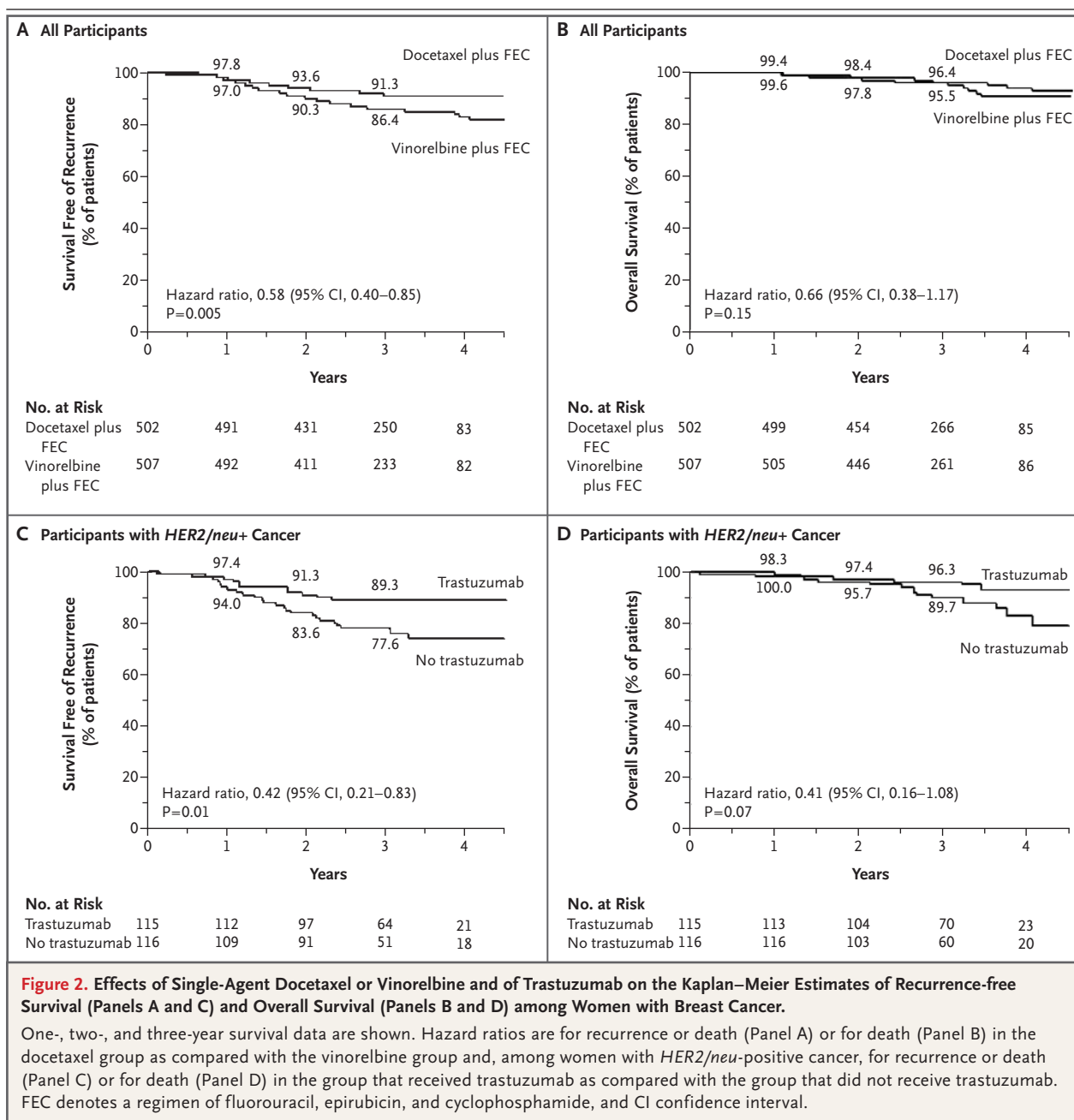
‡ The P value is for grade 1 or 2 as compared with grade 3.

§ One woman who had a tumor with *HER2/neu* amplification did not participate in randomization for trastuzumab.

respectively; the protocol-specified 80-mg dose of docetaxel in 83.3 percent and 81.6 percent of the cycles, respectively; the protocol-specified dose of vinorelbine in 80.3 percent and 71.9 percent of the cycles, respectively; and the protocol-specified dose of epirubicin in 94.0 percent and 92.0 percent of the cycles, respectively.

EFFICACY

Recurrence of breast cancer or death without re-



currence was less common among women treated with docetaxel plus FEC than among those treated with vinorelbine plus FEC (42 of 502 vs. 71 of 507; hazard ratio for recurrence or death, 0.58; 95 percent confidence interval, 0.40 to 0.85; $P=0.005$) (Fig. 2A). The development of distant metastases also was less common in the docetaxel group (33, vs. 58 in the vinorelbine group; hazard ratio, 0.56; 95 percent confidence interval, 0.37 to 0.86; $P=0.008$). The hazard ratios for re-

currence or death in the docetaxel group, as compared with the vinorelbine group, remained similar when adjusted according to center (0.58; 95 percent confidence interval, 0.40 to 0.85) or according to the number of positive nodes (0.57; 95 percent confidence interval, 0.39 to 0.83). Overall survival was not significantly different between the groups (20 patients in the docetaxel group vs. 30 in the vinorelbine group died; hazard ratio for death in the docetaxel group, as compared with

the vinorelbine group, 0.66; 95 percent confidence interval, 0.38 to 1.17; $P=0.15$) (Fig. 2B).

Of the 115 patients in the trastuzumab group who were included in the analysis of efficacy, 12 had a recurrence of breast cancer or died without recurrence, whereas in the control group (116 patients), there were 27 such cases (hazard ratio for recurrence or death in the trastuzumab group, as compared with the control group, 0.42; 95 percent confidence interval, 0.21 to 0.83; $P=0.01$) (Fig. 2C). The hazard ratio remained similar when adjustment was made according to the type of chemotherapy given (0.41; 95 percent confidence interval, 0.21 to 0.82), center (0.42; 95 percent confidence interval, 0.21 to 0.83), or the number of positive nodes (0.39; 95 percent confidence interval, 0.20 to 0.77). Women who received trastuzumab had fewer distant recurrences of cancer than did women who did not receive the antibody (8 vs. 26; hazard ratio, 0.29; 95 percent confidence interval, 0.13 to 0.64; $P=0.002$) (Fig. 3). In addition, their overall survival tended to be better (6 vs. 14 patients died; hazard ratio for death, 0.41; 95 percent confidence interval, 0.16 to 1.08; $P=0.07$) (Fig. 2D).

ADVERSE EFFECTS

Docetaxel was more commonly associated with neutropenic fever, stomatitis, alopecia, nail problems, toxic effects on the skin, allergic reactions,

neuropathy, and edema than was vinorelbine, which more frequently caused peripheral-vein phlebitis and elevation in the serum aspartate aminotransferase level. After the dose of docetaxel was reduced from 100 mg per square meter to 80 mg per square meter, the frequency of neutropenic fever decreased to 14.9 percent ($P<0.001$). Trastuzumab did not significantly increase the frequency of adverse events related to vinorelbine or docetaxel (Table 2).

One patient had cardiac infarction and three had cardiac failure; none of these four patients had received trastuzumab. Left ventricular ejection fractions were preserved in women who received trastuzumab (Table 3). Trastuzumab-treated women had slightly better ejection fractions than those who did not receive trastuzumab; in an ANCOVA model, the estimated difference 12 months after the completion of chemotherapy was 1.7 percentage points (95 percent confidence interval, -0.1 to 3.5 percentage points; $P=0.06$), and at 36 months it was 3.0 percentage points (0.7 to 5.4 percentage points, $P=0.01$). In this model, vinorelbine and docetaxel had similar estimated effects on the ejection fraction at both times ($P=0.50$). Four women treated with trastuzumab (3.5 percent) and seven who were not (6.0 percent) had one or more measurements of ejection fraction more than 15 percentage points less than the pretreatment value. A decrease by

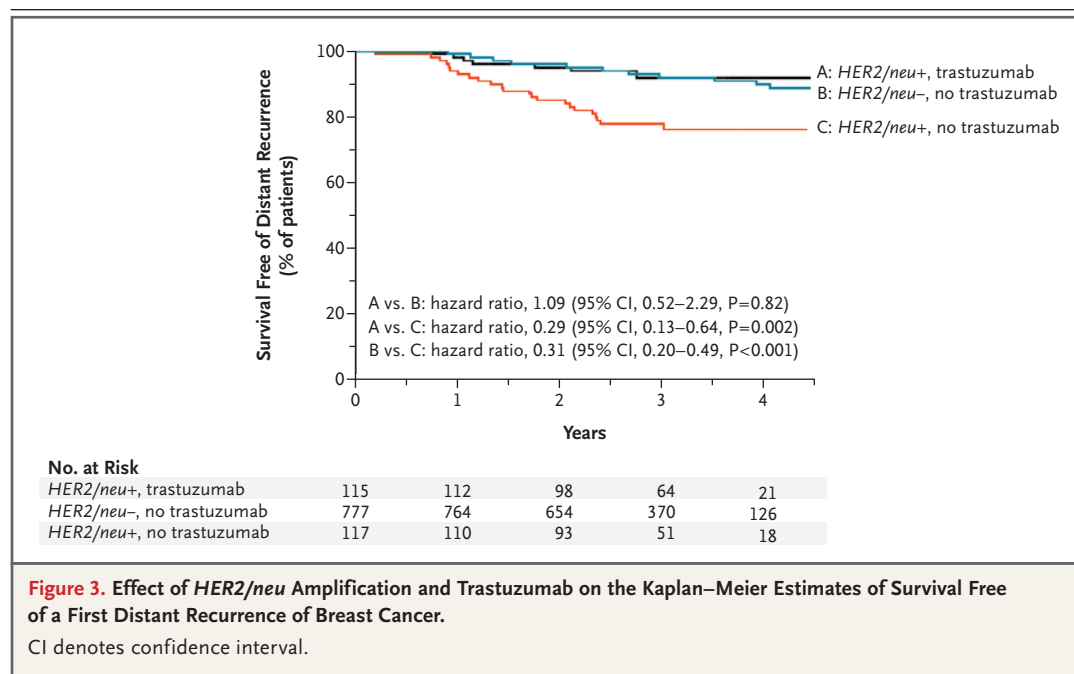


Table 2. Influence of Trastuzumab on Adverse Events Related to Docetaxel and Vinorelbine Treatment.*

Adverse Event	Docetaxel, No Trastuzumab (HER2/neu+ or HER2/neu-, N=447)†		Docetaxel plus Trastuzumab (HER2/neu+, N=54)		Vinorelbine, No Trastuzumab (HER2/neu+ or HER2/neu-, N=446)		Vinorelbine plus Trastuzumab (HER2/neu+, N=61)‡	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
<i>percent</i>								
Anemia‡	66.0	0.5	63.0	0	66.7	0.2	73.8	0
Neutropenia‡	1.6	98.5	0	100.0	28.6	58.3	37.7	55.7
Thrombocytopenia‡	3.7	0	0	0	0.7	0	0	0
Elevated aspartate aminotransferase	19.2	0.2	31.4	0	47.2	0.7	58.3	3.3
Vomiting	10.2	0.5	11.8	0	8.6	0.5	3.3	0
Stomatitis	71.1	2.7	66.0	4.0	40.0	0	50.0	0
Alopecia	98.0	—	100.0	—	52.6	—	50.8	—
Nail problems	55.9	—	47.9	—	9.3	—	16.4	—
Toxic effects on skin (e.g., rash)	55.6	0.9	60.0	0	21.4	0.7	18.0	0
Phlebitis	8.9	0	6.0	0	31.1	0	50.0	0
Allergic reaction	11.7	2.0	13.5	5.8	2.9	0	10.0	0
Infection, no neutropenia	39.2	5.0	43.1	5.9	30.0	2.0	32.8	1.6
Neutropenic fever	0	23.0	0.0	29.6	0	2.9	0	4.9
Neuropathy								
Motor	30.5	1.4	27.5	0	17.7	2.0	13.1	1.6
Sensory	49.5	0.2	57.4	0	43.7	1.1	36.1	0
Edema	61.6	1.6	62.0	0	30.0	0	37.7	0
Fatigue	83.0	8.2	76.0	8.0	81.4	3.2	80.3	4.9
Any adverse effect‡	100.0	100.0	100.0	100.0	100.0	80.9	100.0	75.9

* A dash denotes that the grades were not applicable.

† One patient who did not receive the study treatments was excluded from the analysis.

‡ Results are given for the subgroup of patients (71.3 percent) who had nadir cell counts determined.

Table 3. Left Ventricular Ejection Fraction (LVEF) during Follow-up among Study Participants Who Had Breast Cancer with *HER2/neu* Amplification.*

Treatment Group	Before Chemotherapy	At the Last Chemotherapy Cycle	12 Mo after Chemotherapy	36 Mo after Chemotherapy
Docetaxel plus FEC (N=58)				
LVEF (%)				
Median	67	64	64	64
Range	53–83	48–78	45–79	52–76
No. of patients	56	51	49	24
Docetaxel plus FEC and trastuzumab (N=54)				
LVEF (%)				
Median	66	65	66	69
Range	49–82	51–78	51–83	49–77
No. of patients	50	48	48	30
Vinorelbine plus FEC (N=58)				
LVEF (%)				
Median	65	65	65	63
Range	50–80	46–80	45–78	44–74
No. of patients	53	49	48	22
Vinorelbine plus FEC and trastuzumab (N=61)				
LVEF (%)				
Median	64	63	65	64
Range	47–85	47–85	45–79	53–80
No. of patients	61	60	60	32

* FEC denotes fluorouracil, epirubicin, and cyclophosphamide.

more than 10 percentage points, resulting in an ejection fraction of less than 50 percent, occurred in three patients (none of whom had received trastuzumab).

DISCUSSION

Adjuvant docetaxel, as compared with vinorelbine, improved recurrence-free survival in women with breast cancer. However, docetaxel was more toxic, and the scheduled starting dose was reduced during the study because of adverse effects. The use of granulocyte colony-stimulating factors or prophylactic antibiotics might have reduced the severity of neutropenia. Different doses of docetaxel have not been compared in the adjuvant setting. In this trial, women treated with 100 mg of docetaxel per square meter and those treated with 80 mg per square meter had similar outcomes (data not shown), but this unplanned analysis may have been underpowered.

A short course of adjuvant trastuzumab given

concomitantly with chemotherapy, as compared with chemotherapy alone, was an effective treatment for *HER2/neu*-positive cancer. None of the women who were treated with trastuzumab had cardiac failure, and unexpectedly, these women had slightly better maintenance of left ventricular ejection fraction than did those who did not receive the antibody. Administration of trastuzumab before FEC and radiotherapy as well as the small cumulative dose of epirubicin given may have contributed to the preservation of cardiac function. Regimens containing more than 60 mg of epirubicin per square meter per cycle may have better efficacy than smaller doses,¹⁹ but epirubicin at a dose of 90 mg per square meter, given for four to six cycles with cyclophosphamide and trastuzumab, may frequently decrease the left ventricular ejection fraction and occasionally cause congestive heart failure.²⁰

This prospective study confirms the adverse effect of *HER2/neu* amplification on prognosis. Survival free of distant disease was substantially

less favorable among women with *HER2/neu*-positive cancer who did not receive trastuzumab than among those with *HER2/neu*-negative cancer (Fig. 3). Trastuzumab abrogates much of the adverse effect of *HER2/neu* amplification on outcome.

The proportion of women with *HER2/neu*-positive disease was 23 percent, and thus only 232 women participated in randomization with respect to trastuzumab. The small size of this subgroup and the short duration of the follow-up are limitations of the study. Nevertheless, the number was large enough to allow detection of a statistically significant difference in recurrence-free survival between treatments. When designing the study, we anticipated that *HER2/neu* amplification would be associated with frequent relapses⁴⁻⁶ and that trastuzumab would be effective, according to findings in studies of its use in metastatic disease.⁷ The likelihood of detecting a difference was expected to be further improved by the use of in situ hybridization to determine the number of copies of *HER2/neu* during patient selection and by the concomitant use of potentially synergistic chemotherapy.^{13,14}

The optimal duration of adjuvant trastuzumab therapy is not known and may be clarified only in further randomized trials. Our results indicate

that a nine-week period of trastuzumab administration is effective in women with *HER2/neu*-positive breast cancer. Regimens in which only a few cycles of trastuzumab are administered concurrently with chemotherapy reduce the number of patient visits and may be more cost-effective than regimens that require administration over a period of 12 to 24 months.^{9,10,21} In addition, such regimens may result in few cardiac adverse effects.

Drs. Joensuu and Kellokumpu-Lehtinen report having received compensation for time served on the Sanofi-Aventis advisory board; Dr. Joensuu, compensation for time served on the Roche advisory board; Drs. Joensuu, Kellokumpu-Lehtinen, Bono, Hemminki, and Turpeenniemi-Hujanen, lecture fees from Sanofi-Aventis; and Drs. Joensuu, Kellokumpu-Lehtinen, Bono, Alanko, Isola, and Turpeenniemi-Hujanen lecture fees from Roche. No other potential conflict of interest relevant to this article was reported.

We are indebted to Professor Kaija Holli, Dr. Riikka Huovinen, and Kirsi Rouhento of the Finnish Breast Cancer Group for administrative help; to the members of the study monitoring committee, physician-in-chief Tapani Hakala, physician-in-chief Terhi Hermansson, and Professor Lyly Teppo; to member of parliament Osmo Soininvaara, editor-in-chief Jussi Huttunen, and director general Jorma Huhtanen for their support in obtaining financing of the study; to members of the FinHer Study Group, study nurse Mrs. Kaija Seppälä, and many medical, nursing, and clerical staff members for their support at the participating centers; and to all the women participating in the FinHer trial for their contribution to this research.

APPENDIX

In addition to the authors, the following investigators participated in the FinHer Study: *Helsinki University Hospital, Helsinki*: A.-L. Kautio, L. Teerenhovi, M. Hernberg, and L. Vehmanen; *Tampere University Hospital, Tampere*: T. Korhonen; *Satakunta Central Hospital, Pori*: E. Korkeila; *Oulu University Hospital, Oulu*: G. Blanco and M. Heikkinen; *Seinäjäki Central Hospital, Seinäjoki*: T. Ala-Luhtala; *Kuopio University Hospital, Kuopio*: H. Virsunen; *Joensuu Central Hospital, Joensuu*: R. Kesikikuru; *Rovaniemi Central Hospital, Rovaniemi*: A. Maiche; *Vaasa Central Hospital, Vaasa*: E. Thölix; and *South Karelia Central Hospital, Lappeenranta*: K. Möykkynen — all in Finland.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74-108.
2. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687-1717.
3. Owens MA, Horten BC, Da Silva MM. *HER2* amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. *Clin Breast Cancer* 2004;5:63-9.
4. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the *HER2/neu* proto-oncogene in human breast and ovarian cancer. *Science* 1989;244:707-12.
5. Press MF, Bernstein L, Thomas PA, et al. *HER2/neu* gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas. *J Clin Oncol* 1997;15:2894-904.
6. Ravdin PM, Chamness GC. The *c-erbB-2* proto-oncogene as a prognostic and predictive marker in breast cancer: a paradigm for the development of other macromolecular markers — a review. *Gene* 1995;159:19-27.
7. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against *HER2* for metastatic breast cancer that overexpresses *HER2*. *N Engl J Med* 2001;344:783-92.
8. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 Study Group. *J Clin Oncol* 2005;23:4265-74.
9. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in *HER2*-positive breast cancer. *N Engl J Med* 2005;353:1659-72.
10. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable *HER2*-positive breast cancer. *N Engl J Med* 2005;353:1673-84.
11. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol* 2004;22:322-9.
12. Jahanzeb M. Trastuzumab-based combinations in metastatic breast cancer: how to make a choice. *Clin Breast Cancer* 2003;4:28-38.
13. Pegram M, Hsu S, Lewis G, et al. Inhibitory effects of combinations of *HER2/neu* antibody and chemotherapeutic agents used for treatment of human breast cancers. *Oncogene* 1999;18:2241-51.
14. Pegram MD, Konecny GE, O'Callaghan C, Beryt M, Pietras R, Slamon DJ. Rational combinations of trastuzumab with chemotherapeutic drugs used in the treat-

- ment of breast cancer. *J Natl Cancer Inst* 2004;96:739-49.
15. Isola J, Tanner M, Forsyth A, Cooke TG, Watters AD, Bartlett JM. Interlaboratory comparison of HER-2 oncogene amplification as detected by chromogenic and fluorescence in situ hybridization. *Clin Cancer Res* 2004;10:4793-8.
16. Joensuu H, Alanko T, Bono P, et al. Trastuzumab shows no short-term cardiac toxicity when given concomitantly with single-agent vinorelbine or docetaxel as adjuvant treatment for early breast cancer. *Proc Am Soc Clin Oncol* 2003;22:19a. abstract.
17. Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika* 1977;64:191-9.
18. Lundin J, Lundin M, Isola J, Joensuu H. A Web-based system for individualised survival estimation in breast cancer. *BMJ* 2003;326:29.
19. Bonnetterre J, Roche H, Kerbrat P, et al. Epirubicin increases long-term survival in adjuvant chemotherapy of patients with poor-prognosis, node-positive, early breast cancer: 10-year follow-up results of the French Adjuvant Study Group 05 randomized trial. *J Clin Oncol* 2005; 23:2686-93.
20. Untch M, Eidtmann H, du Bois A, et al. Cardiac safety of trastuzumab in combination with epirubicin and cyclophosphamide in women with metastatic breast cancer: results of a phase I trial. *Eur J Cancer* 2004;40:988-97.
21. Perez EA, Suman VJ, Davidson NE, et al. Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. *J Clin Oncol* 2004;22:3700-4. [Erratum, *J Clin Oncol* 2005;23:1594.]

Copyright © 2006 Massachusetts Medical Society.