VOLUME 27 · NUMBER 36 · DECEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Trastuzumab for Patients With Axillary-Node–Positive Breast Cancer: Results of the FNCLCC-PACS 04 Trial

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Submitted March 16, 2009; accepted July 9, 2009; published online ahead of print at www.jco.org on November 16, 2009.

Supported by The Ligue Nationale Contre le Cancer and Roche Laboratories.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2736-6129/$20.00

DOI: 10.1200/JCO.2009.23.0946

ABSTRACT

Purpose
To evaluate the efficacy of trastuzumab in patients with node-positive breast cancer treated with surgery, adjuvant chemotherapy, radiotherapy, and hormone therapy if applicable.

Patients and Methods
Three thousand ten patients with operable node-positive breast cancer were randomly assigned to receive adjuvant anthracycline-based chemotherapy with or without docetaxel. Patients who presented human epidermal growth factor receptor 2 (HER2) -overexpressing tumors were secondary randomly assigned to either a sequential regimen of trastuzumab (6 mg/kg every 3 weeks) for 1 year or observation. The primary end point was disease-free survival (DFS).

Results
Overall 528 patients were randomly assigned between trastuzumab (n = 260) and observation (n = 268) arm. Of the 234 patients (90%) who received at least one administration of trastuzumab, 196 (84%) received at least 6 months of treatment, and 41 (18%) discontinued treatment due to cardiac events (any grade). At the date of analysis (October 2007), 129 DFS events were recorded. Random assignment to the trastuzumab arm was associated with a nonsignificant 14% reduction in the risk of relapse (hazard ratio, 0.86; 95% CI, 0.61 to 1.22; $P = .41$, log-rank stratified on pathologic node involvement). Three-year DFS rates were 78% (95% CI, 72.3 to 82.5) and 81% (95% CI, 75.3 to 85.4) in the observation and trastuzumab arms, respectively.

Conclusion
After a 47-month median follow-up, 1 year of trastuzumab given sequentially after adjuvant chemotherapy was not associated with a statistically significant decrease in the risk of relapse.

J Clin Oncol 27:6129-6134. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase activated by dimerization.[1] HER2 dimerization leads to activation of intracellular kinase pathways, and ultimately cancer cell proliferation.[2] HER2 is overexpressed in 10% to 20% breast cancer patients.[3] Such overexpression is the consequence of *ERBB2* gene amplification in most cases.[4] Preclinical works have shown that *ERBB2* gene amplification and HER2 overexpression are involved in breast oncogenesis. ERBB2 transgenic mice indeed develop breast cancer,[5] and ERBB2 transfection leads to malignant transformation.[6] These data have led to the development of drugs that aim at inhibiting HER2 activation.[7] Trastuzumab is a HER2-specific monoclonal antibody. This drug improves response rates, progression-free survival, and overall survival in patients with HER2-overexpressing metastatic breast cancer.[8,9] In addition, the administration of trastuzumab in the preoperative setting has been associated with high rate of pathologic complete responses.[10-12] Six randomized trials[12-16] have shown that the administration of trastuzumab in the (neo)adjuvant setting improves progression-free survival, and in most of the trials, overall survival. The administration of trastuzumab was associated with a decrease in left ventricular ejection fraction (LVEF) in all the trials.

Although the administration of trastuzumab in the adjuvant setting is now considered as a standard of care, several questions remain regarding optimal schedule. First, it is not clear whether trastuzumab should be given concomitantly or sequentially to chemotherapy. Second, the duration of administration is still a matter of controversy. One of the studies suggests that short administration could provide a significant reduction in the risk of

relapse.[15] Finally, the optimal chemotherapy regimen to be used before or concomitantly with trastuzumab is not well defined. Regarding this latter point, the optimal use of anthracycline-based chemotherapy is not clear, given the cumulative cardiac toxicity of anthracyclines and trastuzumab, especially when given concomitantly.

In 2001, we initiated the PACS04 trial, a randomized trial performed for patients with axillary node-positive breast cancer. This trial aimed at evaluating the efficacy of concomitant use of docetaxel with anthracyclines, and the efficacy of trastuzumab given for 1 year after the end of adjuvant chemotherapy. In this article, we report results of the second randomization (ie, evaluation of trastuzumab efficacy in the adjuvant setting in HER2-positive patients).

PATIENTS AND METHODS

Patients

The study design and flow chart are presented in Figure 1. The PACS04 trial included a total of 3,010 patients from 82 French and Belgian institutions between February 2001 and August 2004. Women eligible for the study presented an axillary node–positive, nonmetastatic unilateral breast adenocarcinoma. Left ventricular ejection fraction (LVEF) had to be above 50% at time of baseline evaluations (multiple-gated acquisition scan or echocardiography). Other eligibility criteria included age $\geq$ 18 and $\leq$ 65 years, surgical complete resection, normal blood tests. These 3,010 patients were randomly assigned to either six courses of fluorouracil 500 mg/m^2, epirubicine 100 mg/m^2, and cyclophosphamide 500 mg/m^2 ($FE_{100}C$) or epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 (ED_{75}) every 3 weeks. Written informed consent was obtained before randomization. The protocol was reviewed and approved by the ethics committee/institutional review board and the study was conducted according to the Declaration of Helsinski and European Good Clinical Practice requirements.

Patients who presented HER2-overexpressing breast cancer were subsequently randomly assigned between 1 year of trastuzumab and observation. No specific eligibility criteria were required for the second randomization, except positive HER2 status. Second randomization was done as soon as the HER2 status was known. This usually occurred before the completion of the chemotherapy phase. Methods for HER2 determination were standardized for all patients. Eighteen reference centers performed the HER2 determination. HER2 overexpression was defined according to immunohistochemistry and fluorescent in situ hybridization. HER2 overexpression (HER2 3+) by immunohistochemistry was defined as a complete and intense membrane staining in more than 10% tumor cells from the invasive component of the tumor. NCB11 antibody (dilution 1/600; Novocastra Laboratories, Newcastle on Tyne, United Kingdom) was used for immunohistochemistry. The presence of ERBB2 amplification was assessed for 2+ cases only (ie, with a weak to moderate complete membrane staining in > 10% tumor cells of the invasive component of the tumor). ERBB2 amplifications were assessed by fluorescent in situ hybridization (Ventana probe, Ventana Medical System, or Vysis probe, Abbott Laboratories, Abbott Park, IL). ERBB2 amplification was defined as an ERBB2/CEP 17 ratio $\geq$ 2.2.

Treatments

Chemotherapy and radiation therapy were administered before starting trastuzumab. Chemotherapy consisted in either six courses of $FE_{100}C$

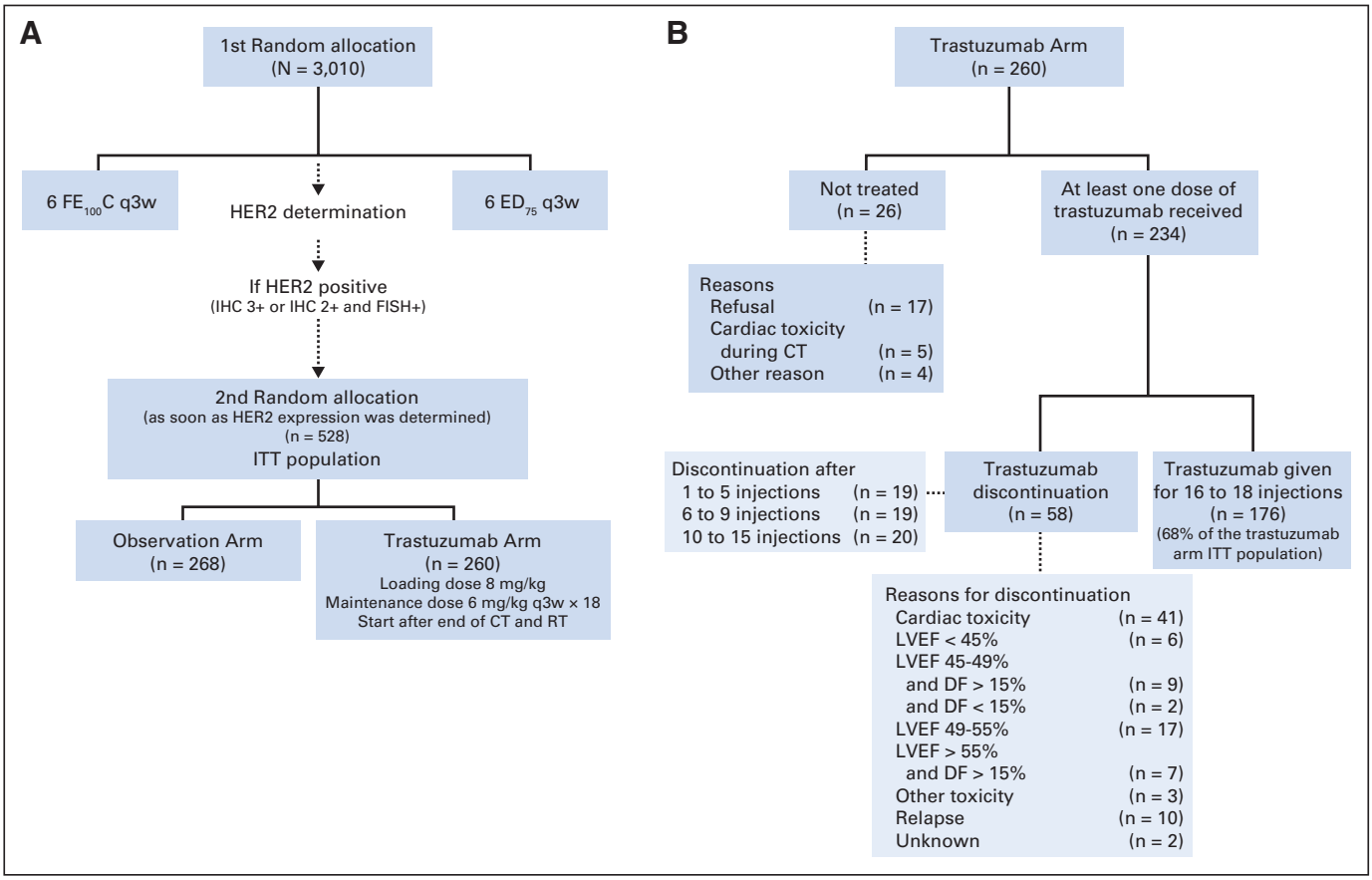

Fig 1. (A) Study design; (B) patient exposure to trastuzumab. HER, human epidermal growth factor receptor; $FE_{100}C$, fluorouacil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2; ED75, epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2; IHC, immunohistochemistry; FISH; fluorescent in situ hybridization; CT, chemotherapy; ITT, intent to treat; RT, radiotherapy; LVEF, left ventricular ejection fraction; DF, decreased fraction.

or ED_{75} regimen. $FE_{100}C$ regimen included fluorouracil 500 mg/m^2, epirubicine 100 mg/m^2, and cyclophosphamide 500 mg/m^2 (at day 1 of a 21-day cycle). ED_{75} regimen included epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 (day 1 = day 21). Radiation therapy was performed within 4 weeks after chemotherapy completion and was mandatory for all patients who had undergone breast-conserving surgery. Endocrine therapy was mandatory for patients with hormone receptor positive disease (estrogen and/or progesterone receptors $\geq$ 10% in immunohistochemistry). Premenopausal patients had to receive tamoxifen 20 mg/d for 5 years. The choice of endocrine therapy (anastrozole or tamoxifen) was left at the discretion of investigator for postmenopausal women. The menopausal status was determined at the beginning of chemotherapy.

Trastuzumab was started after the end of chemotherapy and radiotherapy, and was delivered on a once every 3 weeks schedule. The loading dose was 8 mg/kg (day 1 of the first cycle). Subsequent doses were given at 6 mg/kg every 3 weeks. Trastuzumab administration was planned for 1 year. Trastuzumab was initiated if patients had received at least four cycles of chemotherapy, LVEF was above 55% (or between 50% and 55% if cardiologist approved trastuzumab administration), and if there was no evidence of metastatic disease.

Follow-Up During Trastuzumab Treatment and Rules for Discontinuation

During trastuzumab administration, LVEF evaluation (multiple-gated acquisition scan or echocardiography), clinical examination, and blood tests (CBC, electrolytes) were done at months 1, 2, 5, 8, and 12. No dose reduction was allowed. Trastuzumab was discontinued if the patient decided to stop treatment, in case of cardiac toxicity or other clinical intolerance (at the discretion of the investigator).

Regarding cardiac toxicity, trastuzumab treatment was stopped if LVEF dropped below 45%, or if LVEF was between 45% and 50% together with a relative decrease of 15% or more. If LVEF ranged between 45% and 50% together with a relative decrease less than 15%, or if LVEF ranged between 50% and 55%, a cardiologist's advice was requested to decide about trastuzumab discontinuation. No trastuzumab reintroduction was allowed.

Follow-Up After Trastuzumab Treatment

After trastuzumab administration, patients were seen every 6 months for a clinical exam and blood tests (CBC, electrolytes). LVEF assessment was performed 6 months after the last administration of trastuzumab then at year 5 of follow-up. Complete blood tests (CBC, electrolytes, liver function, creatininemia, calcemia, glycemia), mammography, liver ultrasound, bone scan, and chest x-ray were planned annually for 5 years.

Statistical Analyses and Study Goals

The primary objective of the PACS04 trial was to evaluate the efficacy and tolerance of a combined administration of docetaxel (75 mg/m^2) and epirubicine (75 mg/m^2) as compared to standard $FE_{100}C$ regimen. The second objective was to evaluate the efficacy and tolerance of trastuzumab given for 1 year as sequential treatment after chemotherapy and radiotherapy. The primary end point was disease-free survival (DFS) defined as the time from first randomization to one of the following events: local or regional recurrence, distant metastases, contralateral breast cancer, or death from any cause whichever came first. Patients alive who never experienced either of these events were censored at the last follow-up visit. Secondary end points included safety, event-free survival (DFS + second primary), and overall survival. Sample size was determined according to the second objective (efficacy of trastuzumab). It was hypothesized that trastuzumab would decrease the risk of recurrence by 37%, and that the 3-year DFS rate would be 70% in the observation arm. Based on an absolute improvement of 10% in the 3-year DFS rate (hazard ratio [HR], 0.625), 520 patients were to be randomly assigned to insure an 80% power at the 5% level of significance. Considering that around 10% of the patients randomly assigned in the trastuzumab arm will not receive the drug, the absolute number of patients planned in the trial was 540. Assuming that 20% of patients present an HER2-overexpressing breast cancer, a total of 3,000 patients were to be randomly assigned to the first part of the trial. The final analysis for the second randomization of the trial (trastuzumab question) was planned when 118 events were observed, which were expected to occur after 3 years. Statistical analyses were performed by intent to treat. Survival rates were estimated by the Kaplan-Meier method. The log-rank test was used to compare the treatment groups, stratified on the number of invaded lymph nodes. The proportional hazards assumption was tested by introducing a time-dependent covariate interaction term in the stratified Cox model.

RESULTS

Patient Characteristics

A total of 528 patients from 68 centers were randomly assigned to the trastuzumab part of the PACS04 study (second randomization, Fig 1). Among the 528 patients, 268 were randomly assigned to the observation arm and 260 to the trastuzumab arm; 279 and 249 were previously randomly assigned to receive six cycles of $FE_{100}C$ and ED_{75},

Table 1. Patient Characteristics

Characteristic	Observation (n = 268) No.	%	Trastuzumab (n = 260) No.	%
Median age, years	49		48	
Range	22-64		24-65	
Menopausal status				
Premenopausal	113	56	113	56
Postmenopausal	89	44	88	44
Missing	66		59	
Histology				
Lobular	8	3	10	4
Ductal	249	93	246	95
Other	10	4	4	1
Missing	1		0	
Tumor size, mm				
1-20	129	49.4	106	40.9
> 20	132	50.6	153	59.1
Missing	7		1	
Lymph node				
1-3	151	56	156	60
4+	117	44	104	40
SBR				
I	7	3	9	3
II	85	32	80	31
III	173	65	170	66
Missing	3		1	
Hormone receptor				
Negative (ER and PR)	104	39	109	42
Positive (ER and/or PR)	164	61	151	58
Surgery				
Tumorectomy	175	65	161	62
Mastectomy	93	35	99	38
Planned adjuvant chemotherapy				
$FE_{100}C$	144	54	135	52
ED_{75}	124	46	125	48
HER2 status				
HER2 3+ (IHC)	232	87	230	88
HER2 2+ (IHC) with gene amplification by FISH	35	13	29	12
HER2 negative	1		1	

Abbreviations: SBR, Scarf-Bloom and Richardson prognostic grading system; ER, estrogen receptor; PR, progesterone receptor; $FE_{100}C$, fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2; ED_{75}, epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.

Table 2. Cardiac Toxicities of Observation and Trastuzumab Arms According to Adjuvant Chemotherapy Regimens Reported Until M18 of Follow-Up (end of trastuzumab exposure)

	Observation (n = 268)						Trastuzumab (n = 260)					
	FEC (n = 144)		ED (n = 124)		Total		FEC (n = 135)		ED (n = 125)		Total	
LVEF Decline	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Severe	5	3.5	2	1.6	7	2.6	19	14.1	10	8.0	29	11.1
< 45%	3		1		4		7		3		10	
45%-49% and ≥ 15% decrease	2		1		3		12		7		19	
Moderate: 45%-49%	1	0.7	3	2.4	4	1.6	2	1.5	6	4.8	8	3.1
Mild: 50%-55%	18	12.5	9	7.3	27	10.0	23	17.0	32	25.6	55	21.2
Normal: ≥ 55%	120	83.3	110	88.7	230	85.8	91	67.4	77	61.6	168	64.6

Abbreviations: LVEF, left ventricular ejection fraction; FEC, fluorouracil, epirubicine, cyclophosphamide; ED, epirubicin and docetaxel.

respectively. Patient characteristics were well balanced between the two arms (Table 1). Median age was 48 years (range, 22 to 65), 44% were postmenopausal, 40% had both negative hormone receptors.

Treatment With Trastuzumab

Of the 260 patients randomly assigned to receive trastuzumab, as expected in the statistical plan 26 (10%) did not receive any trastuzumab infusion (Fig 1). The main reason was patient refusal (n = 17) and occurrence of cardiac toxicity (LVEF decline and acute pericarditis in one patient) after exposure to anthracyclines (n = 5). Other reasons were progression (n = 2), second cancer (n = 1), and HER2 negative status (n = 1).

Of the 234 patients who received at least one dose of trastuzumab, 196 patients (75% of the intent-to-treat population and 84% of the treated population) received trastuzumab for a minimum of 6 months (> 9 injections), and 176 patients received at least 16 injections of trastuzumab. Among the 58 patients who discontinued trastuzumab before the 16th injection, 35 were previously treated with the $FE_{100}C$ regimen and 23 with the ED_{75} regimen. The main reasons for the early stop were cardiac events in 41 cases (71%) and progressive disease in 10 cases (17%).

Cardiac Safety Profile

Table 2 summarizes cardiac events in the observation and trastuzumab arms according to the first allocated chemotherapy regimen. Ten patients (3.8%) were randomly assigned to the trastuzumab arm and four patients (1.5%) were randomly assigned to the observation arm experienced a LVEF less than 45% at least once during the 12 months after radiotherapy. In addition, 19 (7.3%) and three (1.1%) patients experienced a LVEF ranging between 45% and 50% associated with a relative decrease of 15% or more, respectively. Overall 29 patients (11.2%) randomly assigned to the trastuzumab arm experienced either a LVEF less than 45%, or a LVEF ranging between 45% and 50% with a relative decrease of 15% or more. Among them, 19 patients (14%) were treated with $FE_{100}C$ and 10 patients (8%) were treated with ED_{75}.

Among the 41 patients who discontinued trastuzumab due to cardiac events (Fig 1), 17 patients had a LVEF less than 50%, and 17 had a LVEF value between 50% and 55%. In seven additional patients, trastuzumab was discontinued because of a LVEF decline over 15%, but the LVEF value at the time of discontinuation was more than 55%. Symptomatic congestive heart failures were reported in one and four patients, respectively, in observation and trastuzumab arm. No death from cardiac causes was reported.

Efficacy

After a median follow-up of 47 months, 129 events were recorded, 70 and 59 in the observation and trastuzumab arms, respectively. First events by event type according to treatment arm are presented in Table 3. Random assignment to the trastuzumab arm was associated with a nonsignificant 14% decrease in the risk of relapse (HR, 0.86; 95% CI, 0.61 to 1.22; $P = .41$, log-rank stratified on number of invaded lymph nodes). The 3-year DFS rates were 77.9% (95% CI, 72.2 to 82.5) and 80.9% (95% CI, 75.2 to 85.3) in the observation and trastuzumab arms, respectively (Fig 2A).

At the time of analysis, 40 deaths were reported (18 in the observation arm and 22 in the trastuzumab arm). Random assignment to the trastuzumab arm was not associated with a significant difference in the risk of death (HR, 1.27; 95% CI, 0.68 to 2.38). The 3-year overall survival rates were 96% (95% CI, 93 to 98) and 95% (95% CI, 92 to 97)

Table 3. Events by Type and Localization According to Randomization Arm

	Observation (n = 268)		Trastuzumab (n = 260)	
Parameter	No. of Patients	%	No. of Patients	%
First events	**70**	**26.0**	**59**	**23.0**
Distant (with or without local or regional)	52	19.0	44	17.0
Local only	5	1.8	6	2.3
Regional (with or without local)	4	1.5	1	0.4
Contralateral breast	3	1.1	5	1.9
Nonbreast cancer death	1	0.4	2	0.8
Contralateral breast cancer	**5**	**1.9**	**8**	**3.0**
Distant*	**61**	**22.8**	**47**	**18.1**
Bone	43	16.0	34	13.1
Lung	27	10.1	32	12.3
Liver	67	25.0	53	20.4
Skin	5	1.9	4	1.5
CNS	8	3.0	11	4.2
Other	1	0.4	7	2.7
Second cancer	**1**	**0.4**	**3**	**1.2**
Any death	**19**	**7.1**	**22**	**8.5**
Breast cancer	18	6.7	20	7.7
Other	1	0.4	3	1.2

NOTE. Bold font indicates statistical significance.
*Patients may present several sites simultaneously.

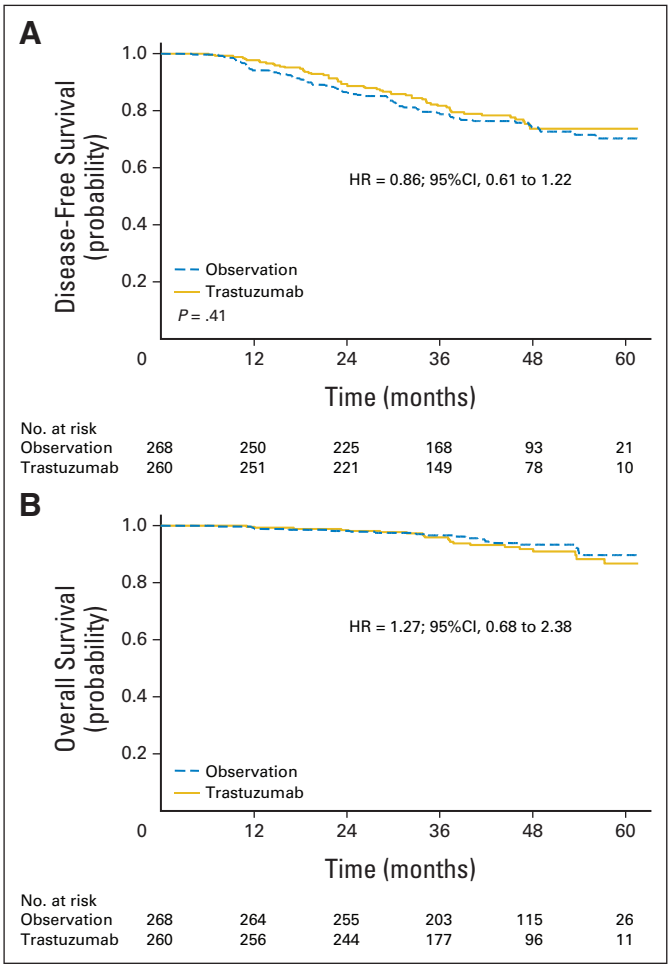

Fig 2. (A) Disease-free survival according to randomization arm. (B) Overall survival according to randomization arm.

in observation and trastuzumab arms, respectively (Fig 2B). More follow-up is needed for a meaningful statistical comparison.

DISCUSSION

All trials that evaluated trastuzumab efficacy in the adjuvant setting have reported a statistically significant benefit. In these trials, risk reductions in the trastuzumab arm ranged between 36% and 58%.[12-16] It must be emphasized that, in addition to these trials, one arm from the North Central Cancer Treatment Group N9831 trial[17] did not report a significant effect of giving trastuzumab as sequential treatment, but this report was unplanned. Several hypotheses could explain why our trial did not report a statistically significant effect of trastuzumab.

Sample size was smaller as compared to four of the five previously reported trials. In addition, 10% of the randomly assigned patients never received trastuzumab treatment, and 38 women received trastuzumab for a duration shorter than 6 months. Nevertheless, the statistical hypothesis was initially based on a 37% reduction in the risk of relapse, a relative effect consistent with previously reported trials,[12-16] and included a provision for 10% of patients untreated with trastuzumab. This consideration suggests that the small sample size does not explain in itself the apparent negative results of this trial. Whether the sequential administration of trastuzumab could explain its apparent lower efficacy is questionable. All trials that evaluated trastuzumab concomitantly to taxanes have reported hazard ratios ranging from 0.42 to 0.61 with a follow-up ranging from 2 to 4 years.[14-16] Three trials, including this one, have evaluated the sequential use of trastuzumab. In the last follow-up analysis of the Herceptin Adjuvant trial, random assigned to the trastuzumab arm was associated with a 36% risk reduction (HR, 0.64; 95% CI, 0.54 to 0.76; $P < .0001$). In the unplanned analysis of the NCCTG 9831 trial,[17] the sequential use of trastuzumab was associated with a nonsignificant 13% risk reduction (HR, 0.87; 95% CI, 0.67 to 1.13). Finally, in this trial, the sequential use of trastuzumab was associated with a nonsignificant 14% reduction in the risk of relapse. Overall, although indirect comparisons of trials cannot provide an answer about the way to administer trastuzumab, it must be acknowledged that the most robust data for trastuzumab efficacy came from trials that evaluated a concomitant schedule. Meta-analyses and planned results of NCCTG 9831 trial will provide more data on whether concomitant use of trastuzumab is better than sequential use. It must be emphasized that preclinical data suggest that, in addition to exerting direct antiproliferative effect on cancer cells, the concomitant use of trastuzumab could increase the taxane sensitivity of cancer cells.[18]

In this study, 25% of treated patients discontinued trastuzumab before the 16th injection. This is higher than in the HERA trial where only 8.5% of the patients discontinued treatment.[12] Nevertheless, these numbers are consistent with those reported in the National Surgical Adjuvant Breast and Bowel Project B31 and North Central Cancer Treatment Group (NCCTG) 9831 trials joint analysis. In this analysis,[13] 31% of the patients who started trastuzumab discontinued treatment before week 52.

In this study, early discontinuation of trastuzumab for cardiac toxicity was slightly higher in patients who previously received FEC_{100} regimen as compared with those treated with ED_{75} regimen as adjuvant chemotherapy. The finding that previous exposure to anthracyclines might increase the cardiac event rate is concordant with findings from the Breast Cancer International Research Group 006 trial. In the second interim analysis of this trial,[16] 18% of patients who received sequential use of anthracyclines and trastuzumab presented a more than 10% LVEF decline. These data highlight the need for a bioassay that predicts which patients with HER2-overexpressing breast cancer derive a high benefit from anthracyclines.

In conclusion, the analysis of the second part of the PACS04 trial did not find an overall statistically significant relapse risk reduction for trastuzumab given as sequential treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Marc Spielmann, Roche Laboratories (C); Jean-Luc Canon, Roche Laboratories (C); Bruno Coudert, Roche Laboratories (C); Frédérique Penault-Llorca, Roche Laboratories (C) **Stock Ownership:** None **Honoraria:** Marc Spielmann, Roche Laboratories; Jean-Luc Canon, Roche Laboratories **Research Funding:** Jean-Luc Canon, Roche Laboratories; Frédérique Penault-Llorca, Roche Laboratories **Expert Testimony:** None **Other Remuneration:** None

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REFERENCES

1. Nahta R, Yu D, Hung MC, et al: Mechanisms of disease: Understanding resistance to HER2-targeted therapy in human breast cancer. Nat Clin Pract Oncol 3:269-280, 2006
2. Rubin I, Yarden Y: The basic biology of HER2. Ann Oncol 12:S3-S8, 2001 (suppl 1)
3. Dendukuri N, Khetani K, McIsaac M, et al: Testing for HER2-positive breast cancer: A systematic review and cost-effectiveness analysis. CMAJ 176:1429-1434, 2007
4. Schaller G, Evers K, Papadopoulos S, et al: Current use of HER2 tests. Ann Oncol 12:S97-S100, 2001 (suppl 1)
5. Takeuchi N, Hiraoka S, Zhou XY, et al: Anti-HER-2/neu immune responses are induced before the development of clinical tumors but declined following tumorigenesis in HER-2/neu transgenic mice. Cancer Res 64:7588-7595, 2004
6. Neve RM, Lane HA, Hynes NE: The role of overexpressed HER2 in transformation. Ann Oncol 12:S9-S13, 2001 (suppl 1)
7. De Laurentiis M, Cancello G, Zinno L, et al: Targeting HER2 as a therapeutic strategy for breast cancer: A paradigmatic shift of drug development in oncology. Ann Oncol 16:iv7-iv13, 2005 (suppl 4)
8. 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 344:783-792, 2001
9. 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 23:4265-4274, 2005
10. Buzdar AU, Ibrahim NK, Francis D, et al: Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 23:3676-3685, 2005
11. Coudert BP, Arnould L, Moreau L, et al: Preoperative systemic (neo-adjuvant) therapy with trastuzumab and docetaxel for HER2-overexpressing stage II or III breast cancer: Results of a multicenter phase II trial. Ann Oncol 17:409-414, 2006
12. Gianni L, Semiglazov V, Manikhas GM, et al: Neoadjuvant trastuzumab in locally advanced breast cancer (NOAH): Antitumour and safety analysis. J Clin Oncol 25:10s, 2007 (abstr 532)
13. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659-1672, 2005
14. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673-1684, 2005
15. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al: Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 354:809-820, 2006
16. Slamon D, Eiermann W, Robert N, et al: BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2neu positive early breast cancer patients. San Antonio Breast Cancer Symposium, San Antonio, TX, December 14-18, 2006 (abstr 52)
17. Perez EA: Further analysis of NCCTG-N9831. Presented at the 41st Annual Meeting of the American Society of Clinical Oncology, May 13-17, 2005, Orlando FL
18. Lee S, Yang W, Lan KH, et al: Enhanced sensitization to taxol-induced apoptosis by herceptin pretreatment in ErbB2-overexpressing breast cancer cells. Cancer Res 62:5703-5710, 2002

