Trastuzumab plus weekly epirubicin and paclitaxel for locally advanced and metastatic breast cancer: preliminary results of a feasibility-phase II study aimed at cardiotoxicity

Cecilia Nisticò[a], Emilio Bria[a], Vanja Vaccaro[a], Federica Cuppone[a], Monica Fornier[d], Isabella Sperduti[b], Armando Carpino[c], Fiorentino Izzo[a], Francesco Tropea[a], Francesco Cognetti[a] and Edmondo Terzoli[a]

A feasibility-phase II study was conducted to assess the cardiotoxicity of weekly trastuzumab, epirubicin, and paclitaxel in patients with human epidermal growth factor receptor-2-positive metastatic breast cancer.
Untreated patients with human epidermal growth factor receptor-2-positive advanced breast cancer received trastuzumab (day 1), and epirubicin (25 mg/m^2) and paclitaxel (80 mg/m^2) (day 2) on a weekly basis. The rate of patients with left-ventricular ejection fraction (L-VEF) reduction greater than 10% after 12 weeks was the primary end point. According to a two-stage model, an initial step with 15 patients was required; after 11 patients without toxicity, a second step with 21 patients was planned. After 255 courses in 15 patients (median treatment weeks: 18), the relative dose intensity was 94.7%. At 12 weeks, three patients (20%) displayed a L-VEF reduction greater than 10%, six and six (40%) patients showed a L-VEF reduction $\leq$ 10% or no change, respectively. Baseline, −12 weeks, and −24 weeks median L-VEF was 69% (range 61–77), 65% (range 60–76), and 65% (range 55–73), respectively. No EKG/cardiac signs were present. Thirteen patients had grade 3 alopecia and two patients had grade 3 asthenia, in the absence of severe hematological toxicity. Objective responses were observed in 11 patients (73.3%, 95% confidence interval 51.0–95.7), with 10 partial. The weekly administration of trastuzumab–epirubicin–paclitaxel is extremely tolerable, also with regard to L-VEF reduction. These results allowed entrance to the second step of the study. *Anti-Cancer Drugs* 20:109–114 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2009, **20:**109–114

Keywords: cardiotoxicity, metastatic breast cancer, trastuzumab, weekly

[a]Department of Medical Oncology, [b]Biostatistics, [c]Cardiology, Regina Elena National Cancer Institute, Rome, Italy and [d]Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, USA

Correspondence to Dr Emilio Bria, Department of Medical Oncology, Regina Elena National Cancer Institute, Via Elio Chianesi 53, Rome 00144, Italy
Tel: +39 0652666222; fax: +39 0652666219;
e-mail: emiliobria@yahoo.it

Cecilia Nisticò and Emilio Bria equally contributed to this study.

Received 8 July 2008 **Revised** 1 October 2008
Accepted 2 October 2008

Introduction

Breast cancer is the most frequently diagnosed cancer in women in the United States (26% of all new cancer cases among women) and accounts for the second most important cause of cancer death in women after lung cancer [1]. Approximately 25–30% of breast cancers exhibit overexpression and/or amplification of the human epidermal growth factor receptor-2 (HER-2) and/or gene, and this particular phenotype provides significant independent prognostic outcome [2,3].

HER-2 is a proto-oncogene that encodes for a transmembrane receptor tyrosine kinase, which plays a dramatic role in growth, differentiation, survival, migration, and neoangiogenesis [4,5]. The recent introduction in clinical practice of the recombinant humanized monoclonal antibody, trastuzumab, which targets directly the extracellular domain of HER-2, has strongly modified the natural history of HER-2 overexpressing breast cancer, with significant clinical benefits regardless of the disease setting [6–8].

In particular, patients with HER-2 overexpressing disease, undergoing therapy with trastuzumab, significantly benefit in terms of both disease-free and overall survival, with a magnitude absolute advantage of 6–7% and 2% at 3 years, respectively [7,8]. Nevertheless, a significant detrimental effect in terms of cardiotoxicity for patients receiving trastuzumab has been confirmed across all trials. According to the National Surgical Adjuvant Breast and Bowel Project Breast-31, the North Central Cancer Treatment Group N9831, and the Herceptin Adjuvant trial updated results, approximately 3.5% and 2.1% of patients developed severe grades III–IV cardiac events [7,8], with a significant reduction (although asymptomatic) of the left-ventricular ejection fraction (L-VEF) rate of 3% [8]. The entire process of the mechanism of both action and toxicity because of trastuzumab is, to date, still far from being completely understood.

The weekly administration of chemotherapeutics represents one of the strategies aimed at optimizing the treatment effect and the chemotherapy tolerability profile.

0959-4973 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e32831bc09b

Certain drugs seem to behave differently when delivered according to schedule; weekly paclitaxel has been shown to be more effective and active than the 'traditional' 3-weekly dosing schedule [9]. Given the increased dose density, which does not compromise the tolerability of the drug, an underlying different mechanism of action according to the schedule is suggested [10,11].

In light of a recently published experience demonstrating the good activity and tolerability (particularly from the cardiac standpoint) of the concurrent weekly administration of epirubicin and paclitaxel regardless of the HER-2 status [12], a feasibility-phase II study properly designed to assess the cardiac safety of such combination and trastuzumab in patients with HER-2 overexpressing disease was conducted.

Patients and methods

Inclusion criteria

Eligibility criteria to enter this phase II study included: untreated histologically proven, locally advanced or metastatic breast cancer overexpressing HER-2 by immuno-histochemistry determination (+ + + Dako Test) or fluorescence in-situ hybridization amplification, life expectancy ≥ 3 months, age between 18 and 75 years, and performance status (Eastern Cooperative Oncology Group Scale) ≤ 2. Other requirements were adequate bone marrow function (absolute neutrophil count $\leq 2 \times 10^3$/dl; platelet count $\geq 100 \times 10^3$/dl; hemoglobin ≥ 9 g/l), adequate liver function (bilirubin concentration ≤ 1.5 times the upper normal limit, aspartate aminotransferase and alanine aminotransferase ≤ 1.5 times the upper normal limit), adequate renal function (creatinine concentration ≤ 1.5 mg/dl; blood urea nitrogen < 50 mg/dl), and cardiac function. Patients with L-VEF $\geq 50\%$ were considered eligible. All metastatic patients did not receive chemotherapy for metastatic setting or had to have progressed 12 months after adjuvant anthracycline-containing chemotherapy. Treatment had to start at least 4 weeks after the end of any previous treatment. Biphosphonates administration for bone metastases was not allowed in the metastatic setting.

Exclusion criteria

Patients with significant cardiac disease or L-VEF of less than 50% were excluded. Patients with symptomatic brain metastases, carcinomatous lymphangitis, neoplastic, and/or pleural effusion as the only site of disease were considered not eligible. Other exclusion criteria included inadequate bone marrow reserve and renal or cardiac insufficiency.

Treatment plan

On day 1, patients were planned to receive weekly trastuzumab of 2 mg/kg/week in 30 min (4 mg/kg for the first administration, over 90 min). On day 2, patients were premedicated with 5-HT3 antagonist intravenously, followed by rapid bolus of epirubicin 25 mg/m^2; after 30 min they received clorphenamine 5 mg intravenously and dexamethasone 8 mg, then, after a further 30 min, they underwent 1-h intravenous infusion of paclitaxel 80 mg/m^2 (1 h after epirubicin), in the outpatient setting. Granulocyte colony-stimulating factor 300 μg subcutaneously was scheduled to be administered 48 and 96 h after chemotherapy administration in a 1-day single dose according to our previous phase II-study with weekly epirubicin–paclitaxel in metastatic breast cancer, in which none of the enrolled 53 patients experienced grades 3–4 hematological toxicity [12]. Granulocyte colony-stimulating factor administered 48 and 96 h after chemotherapy, on the basis of its half-life; chemotherapeutics, pharmacokinetics, and bone marrow function are equally active to a classical schedule in breast cancer in avoiding toxicity and dose intensity maintenance [13].

Weekly chemotherapy was administered without planned treatment interruptions for a maximum of 24 weeks in absence of progressive disease. After 12 weeks of therapy, patients were reevaluated for response. Response evaluation was assessed according to the Response Evaluation Criteria in Solid Tumors criteria [14]. The radiological evaluation included chest radiograph; head, chest, and abdomen computed tomography scan; radionuclide bone scan; and bone MRI, and responses needed to be confirmed after 4 weeks. All patients who received at least one chemotherapy infusion were included in the toxicity evaluation. Complete blood count and blood chemistry tests were evaluated before each treatment. Patients were assessed every week for toxicity according to the National Cancer Institute of Canada–Common Toxicity Criteria (NCIC-CTC) version 3.0.

Cardiac monitoring

The cardiac function was evaluated by complete physical examination, electrocardiography, and echocardiogram examination, which assessed both systolic and diastolic function. L-VEF was determined by applying Teichholz's formula and calculated from the measured left-ventricular end-diastolic diameter and left-ventricular end-systolic diameter, with the mean of three measurements being used. Each study consisted of two-dimensional echocardiography (Echo) and Doppler evaluation. The *E*/*A* ratio was measured to test the diastolic function. Pulsed Doppler volume was calculated at mitral leaflets. Baseline Echo was performed immediately before initiation of the first cycle of chemotherapy, and after 12 and the last weekly administration of chemotherapy. After completion of the treatment, the patients were followed up, performing the examination every 3 months, in the absence of cardiac damage. Patients experiencing a decrease in L-VEF greater than 20% underwent a multigated acquisition scan and discontinued chemotherapy. Patients with the most severely impaired cardiac

function had the most Echos and, thus, including all Echos in the analysis could have biased the results. Therefore, we analyzed the latest Echo obtained from each patient in each period: before, during, and after chemotherapy. The protocol was approved by the local ethics committee. Signed informed consent was required.

Dose modifications

No dose reductions were planned for toxicity. In the presence of hematological toxicity greater than grade 2, treatment was stopped until the WBC recovered to 2.5×10^3/dl and absolute neutrophil count to 1.5×10^3/dl. In the presence of non-hematological toxicity greater than 2, treatment was suspended until recovery to ≤ 1. When grade ≥ 3 toxicity was noted before each drug infusion, the therapy was delayed no more than 2 weeks, otherwise the patient had to be excluded from the study.

Statistics

The primary objective of this feasibility-phase II study was to evaluate the rate of patients with a L-VEF reduction higher than 10% after 12 weeks of treatment. Secondary end points were (i) the median L-VEF reduction estimation; (ii) the clinical cardiac toxicity according to the NCIC-CTC version 3.0; (iii) toxicity other than cardiac; (iv) the objective response rate according to the Response Evaluation Criteria in Solid Tumors criteria [14]; (v) the duration of response (months); and (vi) the progression-free and overall survival. Sample size is computed according to the Simon two-step method design [15]. It is assumed that the treatment will be of no further interest if the reduction of L-VEF ($> 10\%$) is present in more than 30% of patients (P0). The alternate hypothesis (P1) assumes that a reduction of L-VEF in 10% or less of patients would be acceptable. The study was conducted in two stages; the first stage consisted of 15 patients. If more than four L-VEF reduction events had been seen then the trial would have been terminated, otherwise, accrual was to continue to a total of 36 patients (a further 21 patients), with a 5% rejection error and a power of 90%. In the presence of a grades III–IV (severe) cardiotoxicity events according to NCIC-CTC, the study was stopped. Overall survival time was measured from the start of treatment and analyzed by the Kaplan–Meier method [16]. Statistical analyses were performed using SPSS version 13 packages (SPSS Inc., Chicago, Illinois, USA) for Windows.

Results

Patients' characteristics

From January 2003 to November 2006, 15 patients were recruited in the first step of this feasibility-phase II study. Detailed patients' characteristics are listed in Table 1. All patients provided written informed consent.

All patients were evaluable for primary end points, extracardiac toxicity, and response. Overall, 255 courses were delivered in the outpatient setting; the median number of treatment weeks was 18 (range 11–24), with eight patients (53.3%) completing the planned treatment and 13 patients (86.7%) receiving more than 12 weeks of chemotherapy. No further treatment was given after week 24, with the exception of trastuzumab, which was continued until progression. Median delivered dose intensity was high: paclitaxel 75.8 mg/m^2/week (range 58.7–80.0) and epirubicin 23.7 mg/m^2/week (range 18.3–25.0), relative dose intensity for both drugs 94.7% (range 73.3–100).

Cardiac toxicity

A total of 39 Echos (86.7% of the theoretical number) were obtained (mean 2.6 Echos per patient). All patients were evaluable for the primary end point. Three patients (20%) displayed a L-VEF reduction after 12 weeks higher than 10% (10.4, 10.4, and 14.7%, respectively); six and six (40%) patients showed a L-VEF reduction lower than 10% or no change after 12 weeks, respectively (Fig. 1). Baseline median L-VEF was 69% (range 61–77); median L-VEF after 12 weeks was 65% (range 60–76); and median L-VEF after 24 weeks was 65% (range 55–73, calculated on 10 patients) (Fig. 2). Median absolute/relative L-VEF reduction after 12 and 24 weeks were 1.0/1.45% and 4.5/6.5%, respectively. No EKG alteration or cardiac symptoms were present.

Toxicity

Treatment was generally well tolerated, without any dose reductions, hospitalization, or treatment-related deaths. No grades 3–4 hematological toxicity was recorded; 13 patients had grade 3 alopecia, and two patients had grade 3 asthenia.

Activity and survival

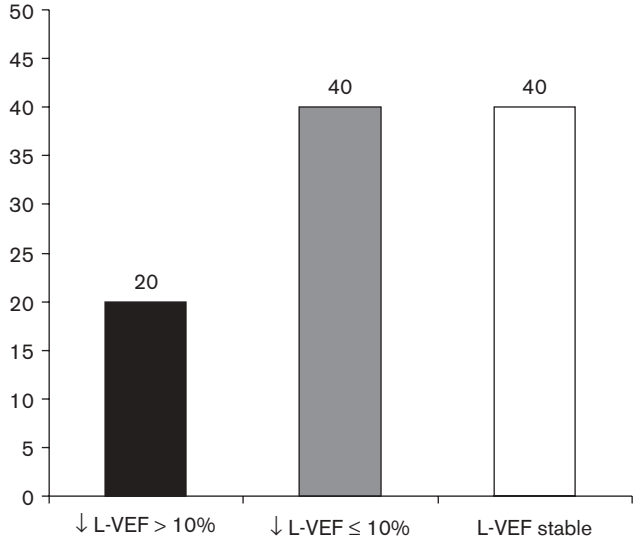
All patients were evaluable for response; objective responses were observed in 11 out of 15 patients

Table 1 Patient characteristics

	Number of patients (total: 15)	%
Median age	47	
Range	27–69	
Performance status (WHO)		
0–1	14	93.3
2	1	6.7
Menopausal status		
Premenopausal status	7	46.7
Postmenopausal status	8	53.3
Hormonal receptor status		
Positive	8	53.3
Negative	7	46.7
Stage		
LABC	4	26.6
MBC	11	73.4
No. of metastatic sites		
1	7	46.6
2	6	40.0
>2	2	13.4

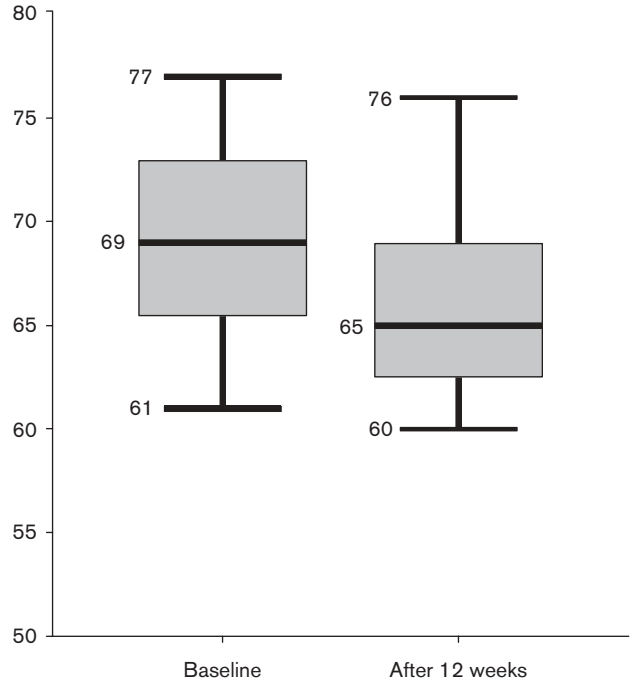
LABC, locally advanced breast cancer; MBC, metastatic breast cancer; WHO, World Health Organization.

Fig. 1



Primary end point patients (%) according to left-ventricular ejection fraction (L-VEF) reduction.

Fig. 2



Secondary end point median left-ventricular ejection fraction (L-VEF) (%).

(73.3%, 95% confidence interval 51.0, 95.7), 10 of which were partial (66.7%) and one complete. Three patients had stable disease (20.0%) and one underwent progression (Table 2). The median duration of the response was 9.0 + months (range 4–21). The median survival was not reached; three deaths occurred because of disease progression. At a median follow-up of 31 months (range 4–64), 3-year progression-free and overall survival were 55.7 and 85.6%, respectively.

Discussion

This study represents one of the earliest attempts to determine the feasibility of the combination of trastuzumab, anthracyclines, and taxanes when treating breast cancer patients with HER-2 overexpressing disease from the cardiological perspective. In light of the evidence from the randomized trials and meta-analyses regarding this issue, we focused our attention upon the reduction of the L-VEF, which has been recognized to be the critical clinical parameter, which 'mirrors' the cardiac effect of the monoclonal antibody.

Although 20% of the enrolled patients showed a L-VEF reduction higher than 10% (in the absence of any other cardiac sign and/or symptoms), the results of the first step of our feasibility-phase II study allowed continuing to the second step (Fig. 1). Although a definite conclusion cannot be reached in the context of the first step of a feasibility-phase II study, our data seem to provide 'reassurance' about the cardiac feasibility of the combination of trastuzumab, anthracyclines, and paclitaxel, at least in a weekly manner. The overall median L-VEF relative reduction of 1.45 and 6.5% at 12 and 24 weeks, respectively, does not seem to be dramatic, also considering the recent data regarding the reversibility of trastuzumab-related cardiotoxicity [17–19]. Of course, these data must be considered relevant to the weekly administration of epirubicin and paclitaxel only, and cannot be applied to different schedules.

Indeed, we previously reported how such a combination in a breast cancer population unselected for HER-2 overexpression, was extremely tolerable, by monitoring the cardiac function with clinical, instrumental, and serological (troponin T and myoglobin) parameters [20].

Nevertheless, patients who develop a L-VEF reduction need to be strictly monitored. Indeed, the pivotal,

Table 2 Response evaluation (RECIST criteria)

	Evaluable population (15 patients)	
	Patients number	% (95% CI)
Overall response rate	11	73.3 (51.0, 95.7)
Partial response	10	66.7
Complete response	1	6.7
Stable disease	3	20.0
Progression	1	6.7

CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors criteria.

randomized trial of trastuzumab combined with chemotherapy for metastatic breast cancer patients showed a high incidence of congestive heart failure among patients who had received trastuzumab and anthracycline-based therapy simultaneously [21].

In a randomized-phase II trial, patients receiving docetaxel–trastuzumab were more likely to experience an asymptomatic L-VEF reduction, when compared with the docetaxel-alone arm (17 vs. 8%, respectively); nevertheless, 12 of the 15 patients who experienced such decrease in the combination arm had received earlier anthracyclines [22].

In the adjuvant setting, where anthracyclines and taxanes are used in almost all trials conducted with trastuzumab, a literature-based meta-analysis, recently demonstrated that a 1.6% absolute significant difference of grades III–IV congestive heart failure, and a 7.2% absolute significant difference of L-VEF reduction were found in those trials administering trastuzumab for 1 year [6]. Therefore, it seems that the 'huge' impact of trastuzumab in terms of efficacy, is in some way 'obscured' by this small effect on cardiac function, which is consistent across all conducted trials and independent of the disease setting.

From a methodological perspective, the hypothesis which allows entrance to the second step of the study has been biased by the pivotal data on cardiotoxicity of such a combination [21]: in the presence of 27% clinical cardiotoxicity, the unacceptable level for L-VEF should have been higher, at least that was the idea before the release of the adjuvant data. Conversely, only the National Surgical Adjuvant Breast and Bowel Project Breast-31 study later reported a L-VEF reduction higher than 10% in 34% of patients [23], which has to be considered the worst ever published result for trastuzumab administered with anthracyclines and taxanes. Subsequently, the other adjuvant trials showed a L-VEF reduction in 15–20% of patients [7,8,24,25], rendering our 20% more realistic, even if more caution in the conduct of the second step is adopted. Anyway, the other secondary end points (i.e. other cardiotoxicities, the absolute median reduction of L-VEF, etc.) seem reassuring.

Preclinical data suggest that HER-2 activation is fundamental for protecting cardiac cells from the damage induced by anthracyclines [26]; this process is likely to determine a new entity of drug-induced cardiac dysfunction, which is different from the anthracycline-myocardial damage [27,28]. Nevertheless, the combination of drugs with the very same overlapping toxicity, although with different mechanisms, represents a difficult problem to overcome. However, as a result of new advances in the discovery of different molecular phenotypes of breast cancer, we might be entering a scenario in which it is likely that fewer patients will be receiving anthracyclines, and even less trastuzumab and anthracyclines [25].

The extremely tolerable profile of weekly epirubicin and paclitaxel motivated our group to test this regimen in combination with trastuzumab as well. The second step of the trial is ongoing, to guarantee both a larger and more reliable sample and to determine the full effect of adverse cardiac events at a longer follow-up, even taking into account all the methodological and power limitations of a such a small sample. Future analysis of patients who experienced cardiac dysfunction (if any) in this trial may reveal new prognostic or predictive indicators of cardiac dysfunction to tailor treatment selection for patients with HER-2-positive breast cancer.

References

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, *et al*. Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**:71–96.
2 Gusterson BA, Gelber RD, Goldhirsch A, Price KN, Save-Soderborgh J, Anbazhagan R, *et al*. Prognostic importance of c-erbB-2 expression in breast cancer. International (Ludwig) Breast Cancer Study Group. *J Clin Oncol* 1992; **10**:1049–1056.
3 Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987; **235**:177–182.
4 Gschwind A, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases: targets for cancer therapy. *Nat Rev Cancer* 2004; **4**:361–370.
5 Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, *et al*. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989; **244**:707–712.
6 Bria E, Cuppone F, Fornier M, Nistico C, Carlini P, Milella M, *et al*. Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: the dark side of the moon? A meta-analysis of the randomized trials. *Breast Cancer Res Treat* 2008; **109**:231–239.
7 Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, *et al*. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353**:1673–1684.
8 Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, *et al*. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007; **369**:29–36.
9 Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, *et al*. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol* 2008; **26**:1642–1649.
10 Gonzalez-Angulo AM, Hortobagyi GN. Optimal schedule of paclitaxel: weekly is better. *J Clin Oncol* 2008; **26**:1585–1587.
11 Seidman AD. "Will weekly work"? Seems to be so. *J Clin Oncol* 2005; **23**:5873–5874.
12 Nistico C, Bria E, Cuppone F, Fornier M, Sperduti I, Carpino A, *et al*. Weekly epirubicin and paclitaxel with granulocyte colony-stimulating factor support in previously untreated metastatic breast cancer patients: a phase II study. *Anti-Cancer Drugs* 2007; **18**:687–692.
13 Papaldo P, Lopez M, Marolla P, Cortesi E, Antimi M, Terzoli E, *et al*. Impact of five prophylactic filgrastim schedules on hematologic toxicity in early breast cancer patients treated with epirubicin and cyclophosphamide. *J Clin Oncol* 2005; **23**:6908–6918.
14 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**:205–216.
15 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10**:1–10.
16 Kaplan EL, Meier P. Nonparametric estimation for incomplete observation. *J Am Stat Assoc* 1958; **53**:475–481.

17 Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol* 2004; **22**:322–329.
18 Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, *et al*. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20**:1215–1221.
19 Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, *et al*. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005; **23**:7820–7826.
20 Nistico C, Bria E, Cuppone F, Carpino A, Ferretti G, Vitelli G, *et al*. Troponin-T and myoglobin plus echocardiographic evaluation for monitoring early cardiotoxicity of weekly epirubicin-paclitaxel in metastatic breast cancer patients. *Anti-Cancer Drugs* 2007; **18**:227–232.
21 Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, *et al*. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344**:783–792.
22 Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, *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**:4265–4274.
23 Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, *et al*. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; **23**:7811–7819.
24 Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, *et al*. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 2008; **26**:1231–1238.
25 Slamon D, Eiermann W, Robert N. –006 oboB. 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/ETH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients. In: Proceedings of San Antonio Breast Cancer Symposium (SABCS), Edition San Antonio (TX, US): Breast Cancer Research and Treatment 2006.
26 Crone SA, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y, *et al*. ErbB2 is essential in the prevention of dilated cardiomyopathy. *Nat Med* 2002; **8**:459–465.
27 Sawyers CL. Will kinase inhibitors have a dark side? *N Engl J Med* 2006; **355**:313–315.
28 Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol* 2005; **23**:2900–2902.