ANTICANCER RESEARCH *24*: 2487-2494 (2004)

Tumor Shrinkage Evaluation During and After Preoperative Doxorubicin and Cyclophosphamide Followed by Docetaxel in Patients with Breast Cancer

FABIO PUGLISI[1], MAURO MANSUTTI[2], GIUSEPPE APRILE[3], ALESSANDRO MARCO MINISINI[1], CARLA DI LORETO[4], MASSIMO BAZZOCCHI[5], VIVIANA LONDERO[5], CARLA CEDOLINI[6], GIULIANA GENTILE[7], STEFANO PIZZOLITTO[8], ANDREA PIGA[3] and ALBERTO SOBRERO[9]

[1]Clinical Oncology, Breast Unit, University of Udine, Udine; [2]Oncology Division, General Hospital, Udine; [3]Clinical Oncology, University of Udine, Udine; [4]Anatomic Pathology, Breast Unit, University of Udine, Udine; [5]Radiology, Breast Unit, University of Udine, Udine; [6]Surgery, Breast Unit, University of Udine, Udine; [7]Surgery Division, General Hospital, Udine; [8]Anatomic Pathology, General Hospital, Udine; [9]Medical Oncology, S. Martino Hospital, Genoa, Italy

Abstract. *Aim: To evaluate the relative activity of the sequential administration of doxorubicin and cyclophosphamide (AC) followed by docetaxel alone, as primary systemic therapy in patients with breast cancer, using an in vivo chemosensitivity predictive assay. Patients and Methods: Patients with stage II-III breast cancer received two cycles of AC (60/600 mg/m^2 every 3 weeks) followed by two cycles of docetaxel (100 mg/m^2 every 3 weeks). All patients underwent comprehensive breast imaging prior to chemotherapy, after two AC and after docetaxel. Results: Forty-two patients were accrued and evaluated by intention-to-treat analysis. After two cycles of AC, the median tumor shrinkage was 18.3%, whereas treatment with docetaxel provided an additional median tumor shrinkage of 34.2%. Pathological complete remission was observed in 5 patients (11.9%), whereas 26 patients (61.9%) experienced a partial response. Conclusion: The relative contribution of docetaxel to tumor mass reduction seemed to be greater than that of AC. However, the slow rate of tumor shrinkage observed may indicate that the activity of the first 2 cycles of AC is carried over into the part of treatment with docetaxel.*

The use of primary systemic therapy (PST) was first introduced into clinical practice in the 1970s, with the aim of achieving operability in patients with locally advanced inoperable breast cancer (1). Subsequently, in the late 1980s, it was also proposed for the treatment of large operable breast cancer with the aim of improving the rate of breast-conserving surgery (1). The growing popularity of PST led to comparative studies of the same regimen given before or after surgery. These trials did not show significant differences in disease-free or overall survival (2-6) between the approaches, thereby supporting the use of PST as an alternative to adjuvant chemotherapy for patients with operable breast cancer enabling less extensive surgery.

There are two potential advantages to PST. First, the activity of the agents to be used as adjuvant treatment may be tested *in vivo* and translational studies may strengthen this approach towards the individualized selection of therapy (7-9). Second, the observation that the response to PST may positively correlate to disease-free survival and to overall survival suggests the adoption of pathological complete response (pCR) rate as an early surrogate endpoint in clinical trials (2,10,11).

In the advanced setting, doxorubicin and docetaxel are among the most effective agents against breast cancer (12,13). In addition, the evidence that the two drugs are only partially cross-resistant (14-16) has supported the development of new regimens containing the combination or sequence of anthracycline and docetaxel in the adjuvant (17,18) as well as in the neoadjuvant setting (19,20).

Since solid tumors are generally sensitive to chemotherapy during the first few cycles of treatment, we thought that giving two cycles of AC and then 2 cycles of docetaxel would have allowed us to determine, in a reasonable time, their different activity. The knowledge of the relative contribution of AC and docetaxel to the overall tumor shrinkage of the entire neoadjuvant program may

Correspondence to: Fabio Puglisi, MD, PhD, Clinica di Oncologia Medica, Policlinico Universitario, Piazzale SM Misericordia, 33100 Udine, Italy. Tel: +39-0432-559304, Fax: +39-0432-559305, e-mail: fabio.puglisi@med.uniud.it

Key Words: Breast cancer, doxorubicin, cyclophosphamide, docetaxel.

serve as a guide to the individualized selection of the best agent to be used adjuvantly, if needed.

Patients and Methods

Female patients, aged 18-75 years, with histologically confirmed invasive breast carcinoma and minimum tumor diameter ≥ 2 cm by physical examination or breast imaging (mammography and/or ultrasound and/or magnetic resonance), were eligible for the study. Preoperative histological diagnosis, hormonal receptor status by H-score (21) and tumor grade (22) were evaluated on 14-gauge core biopsy. The other eligibility criteria were as follows: performance status < 2 according to the Eastern Cooperative Oncology Group scale, adequate bone marrow function, liver function (AST and ALT ≤ 2.5 times the upper normal limit [UNL] and alkaline phospatase ≤ 3 times the UNL) and kidney function (creatinine), normal left ventricular ejection fraction (LVEF) by bi-dimensional echocardiography at rest, no evidence of metastasis at baseline by bone scan, liver ultrasound and two-view chest X-ray, no previous treatment for breast cancer, no previous or concomitant malignancy, absence of symptomatic grade ≥ 2 peripheral neuropathy, no contraindications to corticosteroid therapy and adequate non-hormonal contraception therapy for premenopausal women. Four centers were involved in the recruitment and treatment of patients.

In order to evaluate antitumor activity, maximum tumor size was estimated by a triple assessment (mammography, ultrasound and magnetic resonance) before the start of preoperative chemotherapy, then after two and four cycles of preoperative chemotherapy.

All the procedures followed during the study were in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Written informed consent was obtained from all participants before enrolment in the study.

Treatment. Patients were treated sequentially with two cycles of AC (doxorubicin 60 mg/m^2 by intravenous bolus and cyclophosphamide 600 mg/m^2 by intravenous bolus q21 days), followed by two courses of D (docetaxel 100 mg/m^2 by 1-hour intravenous infusion q21 days) as upfront preoperative chemotherapy. Oral prednisone (50 mg) was administered 12 h and 1 h before therapy, as well as at 12, 24 and 36 h after therapy with docetaxel. Complete blood count was determined on day 1 of each cycle and treatment was permitted if the absolute neutrophil count was > 1,500/mm^3 and platelet count > 100,000/mm^3. Treatment administration was delayed for up to 1 week in the event of neutropenia, thrombocytopenia or mucositis ≥ grade 2. The use of G-CSF was allowed as prophylaxis in patients who developed febrile neutropenia, or for treatment delay of more than one week for neutropenia. If the patient experienced neutropenic fever, the dose of all drugs at the subsequent cycle was reduced by 25%. Patients experiencing a hypersensitivity reaction to docetaxel were treated with AC for two additional cycles before surgery. The dose intensity of each drug was calculated by dividing the total dose (mg/m^2) administered by the time on treatment (weeks). According to an intent-to-treat analysis, cycles that were not given because of patient withdrawals were accounted for by considering 21 days of treatment and a 0 dose of each drug.

Following PST, patients underwent breast surgery that consisted of breast-conserving surgery (quadrantectomy) if the residual tumor size was < 2.5 cm, or modified radical mastectomy if the tumor size was ≥ 2.5 cm. Surgery was performed approximately 21-35 days after the last (fourth) cycle of preoperative chemotherapy. Decisions about adjuvant therapy were left at the discretion of the investigator and based on standard guidelines. However, as suggested by the protocol, the choice of adjuvant chemotherapy (anthracycline-based *vs* docetaxel-based therapy) should be tailored on the basis of relative clinico-radiological response to preoperative chemotherapy as well as toxicity experienced by the patients during the different parts of the neoadjuvant treatment. Hormonal therapy with tamoxifen 20 mg/day for 5 years was given to patients presenting hormone receptor-positive tumors, as evaluated by immunohistochemistry on core biopsy. Patients undergoing quadrantectomy received standard radiotherapy to the remaining breast. Decisions about postmastectomy radiotherapy of the chest wall (with or without regional lymph nodes) were taken on the basis of tumor size before starting PST. The validity of this approach was confirmed in a recently published study (23).

Statistical analysis. Although the primary endpoint of this study was to evaluate the relative activity (% tumor shrinkage) of AC and docetaxel given in a sequential fashion, as PST in patients with breast cancer (observational study), we linked the sample size calculation to the clinical activity of the entire neoadjuvant program in order to protect our patients from unexpectedly low activity. The rate of pCR was used as an indicator of activity. We used the Simon's two-stage design that tested the null hypothesis (H0; the true pCR rate is ≤ 5%) *versus* the alternative hypothesis (H1; the true pCR is ≥ 20%). With this assumption, the alpha level of the design (*i.e.*, the probability of rejecting the null hypothesis when true) was 0.05 and the power 0.9. For a total of 38 required patients, 29 would be accrued during stage 1 and 9 during stage 2. Given a 'true' response probability of 5%, there was a 57.08% probability of ending the study at stage 1. On the other hand, if the 'true' response probability was 20%, then there was a 1.28% probability that the trial was stopped at stage 1. If 1 or fewer pCR were observed during the first stage, then the study would be stopped early. If 4 or fewer pCR were observed by the end of the study, then no further investigation of the drug would be warranted. Taking into consideration 10% potential drop-outs, the study enrolled a total of 42 patients. For percentages relative to response rates, 95% exact binomial confidence limits (95%CL) were calculated.

Association between categorical variables were evaluated by using the Chi-squared test or Fisher's exact test as appropriate. The non-parametric Kruskall Wallis one-way analysis of variance was used for comparison of multiple groups with ordinal data.

All patients were evaluated for efficacy and toxicity on an intention-to-treat analysis.

Assessment of response. Serial imaging (mammography and/or ultrasound and/or magnetic resonance) evaluation of tumor size was performed before PST (baseline), after two cycles of chemotherapy and after the fourth cycle of chemotherapy. Tumor size was calculated by uni-dimensional measurement of the maximum diameter of each tumor. Tumor shrinkage after two cycles was calculated as the difference between the maximum tumor diameter at baseline and the maximum tumor diameter after two AC/ the maximum tumor diameter at baseline x 100. Tumor shrinkage after four cycles was calculated as the difference between

Table I. *Patient and disease characteristics at baseline.*

	Patients (n=42)	
Patient characteristic	No.	%
Menopausal status		
premenopausal	26	62
postmenopausal	16	38
ECOG performance status		
Median	0	100
Histology		
ductal	34	81
lobular	5	12
mixed ductal lobular	3	7
Clinical tumor status		
T1	0	-
T2	30	71
T3	12	29
Maximum radiological diameter (mm)		
Median	35	
Range	16-70	
Maximum clinical diameter (mm)		
Median	40	
Range	18-90	
Palpable axillary nodes	20	48
Estrogen receptor		
positive	23	55
negative	17	40
unknown	2	5
Progesterone receptor		
positive	19	45
negative	21	50
unknown	2	5
Tumor grade on core biopsy		
G1	2	5
G2	22	52
G3	12	29
unknown	6	14

the maximum tumor diameter at baseline and the maximum tumor diameter after PST/ the maximum tumor diameter at baseline x 100. The tumor shrinkage obtained with the last 2 cycles of PST was calculated as the difference between the maximum tumor diameter after two AC and the maximum tumor diameter after two cycles of docetaxel/ the maximum tumor diameter after two AC. According to the RECIST (response evaluation criteria in solid tumors) categories (24), responses after the entire treatment were classified as complete response (CR: tumor shrinkage=100%), partial response (PR: tumor shrinkage ≥ 30%) and no response (NR: tumor shrinkage < 30%).

The modified Chevallier's classification (25) was used for detailed pathological response evaluation: Category 1: disappearance of all tumor either on macroscopic or microscopic assessment; Category 2: presence of *in situ* carcinoma; Category 3: presence of invasive carcinoma with stromal alteration, such as sclerosis or fibrosis; Category 4: no or few modifications of the tumor appearance.

Results

Patient characteristics. From December 1999 to December 2002, 42 patients (median age 47.5 years, range 26-67) with breast cancer ≥ 2 cm entered the trial. The main patients' and tumor characteristics are reported in Table I. Pretreatment radiological tumor size averaged 38.6 mm and clinically-positive axillary nodes were observed in 20 patients (48%).

Treatment administration. In total, 164 cycles of chemotherapy (87 of AC and 77 of docetaxel) were administered during the study. The median dose intensity of AC was 20/200 (range 15-20/150-200) mg/m^2/week. The median dose intensity of docetaxel was 33 (range 0-33) mg/m^2/week. Four patients after the first cycle of AC required one-week delay in treatment because of neutropenia and one patient required a 25% dose reduction of the second cycle of AC because of previous febrile neutropenia. Two patients refused further chemotherapy after 2 AC and underwent anticipated surgery because of anxiety. In one patient, clinical tumor progression was observed after the first cycle of AC and treatment changed to three cycles of docetaxel. Two patients experienced hypersensitivity reaction during docetaxel: the taxane was discontinued and two additional cycles of AC were given.

Efficacy. The median tumor shrinkage after the PST was 48.3% (range –66.6-100, 25th-75th percentiles 32.6-79.16), with a median tumor shrinkage of 18.3% after the first two cycles of AC (range 0-100, 25th-75th percentiles 14.3-33.3). Treatment with docetaxel provided an additional median tumor shrinkage of 34.2% (range–426.3-100, 25th-75th percentiles 17.5-67.5).

According to the RECIST categories, an overall response (CR + PR) rate of 73.8% (95%CL, 57.9-86.1%) was observed. A pCR was observed in 5 patients (11.9%; 95%CL, 3.9%-25.6%), whereas 26 patients (61.9%; 95%CL, 45.6-76.4%) experienced a partial response. In a patient with no pathological evidence of invasive tumor, the presence of ductal carcinoma *in situ* and involvement of the axilla was observed (exact pCR rate: 9.5%; 95%CL, 2.6%-22.6%). A very good response was observed in three additional patients with a residual tumor smaller than 1 mm (all 3 patients) and the presence of lymph node micrometastasis (one patient). One patient experienced a very early clinical progression after the first cycle of AC

Table II. *Relationship between hormone receptor status or tumor grade and decrease in tumor size after preoperative chemotherapy.*

Variable	Median tumor shrinkage after 2 AC (%)	Median tumor shrinkage with docetaxel (%)	Median tumor shrinkage after PST (%)
ER-negative	28.6	82.4	93.7
ER weakly-positive	16.6	26.6	51.1
ER-positive	15.5	22.5	37.5
P value	0.03	0.005	0.001
PGR-negative	25	67	73.3
PGR weakly-positive	14.6	13.9	32.5
PGR-positive	16.6	26.6	37.5
P value	0.32	0.007	0.006
Grade 1	8.3	33.3	40
Grade 2	16.6	33.3	40
Grade 3	26.8	76	89.4
P value	0.12	0.08	0.08

Table III. *Number and percentage of patients experiencing adverse events during AC or docetaxel.*

	AC (n=42)		Docetaxel (n=38)	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Hematological	n (%)	n (%)	n (%)	n (%)
Neutropenia	12 (28.6)	26 (61.9) (2 neutropenic fever)	4 (10.5)	24 (63.1) (3 neutropenic fever)
Anemia	19 (45.2)	-	27 (71)	-
Thrombocytopenia	4 (9.5)	-	1 (2.6)	-
Non-hematological				
Asthenia	12 (28.5)	1 (2.3)	20 (52.6)	1 (2.6)
Hypersensitivity	- -	-	2/42 (4.7) (mild)	
Nail changes	1 (2.3) -	-	5 (13.1) (mild)	
Diarrhea	5 (11.9)	-	9 (23.6)	-
Nausea	28 (66.6)	1 (2.3)	11 (28.9)	-
Vomiting	11 (26.2)	1 (2.3)	-	-
Stomatitis	28 (66.6)	-	25 (65.7)	-
Neurotoxicity (sensorial)	3 (7.1)	-	14 (36.8)	-
Neurotoxicity (motor)	1 (2.3)	-	2 (5.2)	-
Skin rashes	-	-	1 (2.6)	-
Myalgias	-	-	9 (23.6)	-
Alopecia	42 (100)	-	38 (100)	-

(imaging not performed) but obtained a partial response after switching to three cycles of docetaxel. Another patient experienced tumor progression during treatment with docetaxel (tumor shrinkage: –426.3%) and, at the end of the PST, had a progressive disease (final tumor shrinkage: –66.6%). Eleven (55%; 95%CL, 31.5-76.9%) of the 20 patients with pretreatment palpable axillary nodes had pathologically negative lymph nodes after PST.

According to the modified Chevallier's classification, response was reported as 1 in 4 cases (9.5%), 2 in 1 case (2.4%), 3 in 32 cases (76.2%) and 4 in 5 cases (11.9%). No correlation was found between maximum tumor size at baseline and tumor shrinkage after PST. Pretreatment ER status, PGR status and tumor grade were associated with tumor shrinkage as shown in Table II. In addition, a statistically significant association was found between pretreatment ER/PGR status and tumor grade and response as evaluated by RECIST (Chi-square *p* value=0.03). All pCR were observed in patients with ER/PGR-negative and G3 tumors.

Twenty-nine patients (69%) underwent modified radical mastectomy and 13 patients (31%) underwent breast-conserving surgery.

Toxicity. The regimen was feasible and generally well-tolerated. The incidence of hematological and non-hematological toxicity is reported in Table III.

As expected, neutropenia was the most common adverse event, occurring in 90% of patients with AC and in 74% of patients with docetaxel. Among the other clinically relevant adverse events, stomatitis and alopecia were equally distributed in each sequence of the treatment, nausea was more frequent with AC; asthenia, diarrhea, myalgias, neurotoxicity and nail changes were more frequent with docetaxel. In contrast with data from previous studies, no cases of acral erythema (hand-foot syndrome) were observed. The latter side-effect, in fact, was previously ascribed to the sequential use of doxorubicin and docetaxel (26).

Discussion

In general, the clinical response of solid tumors to chemotherapy occurs fairly rapidly. While the time to maximal tumor shrinkage may vary widely, the median time to response is similar among various types of cancers. Breast cancer is not substantially different, with values ranging between 2 and 3 months (27,28). The primary goal of our study was to investigate the relative contribution of 2 AC followed by 2 docetaxel to the overall tumor shrinkage in an attempt to select the most active regimen to be used on an individual basis as adjuvant therapy, if needed. The working hypothesis rested on two assumptions : a) that 2 cycles were enough to have an early assessment of activity and b) that there was no carry over effect of the first treatment to the outcome of the second. If our assumptions were true, a certain number of patients should have shown more sensitive to the first 2 cycles and another group more sensitive to the second. Only 4 patients out of 42 were more sensitive to AC, two patients had similar responses during the two segments of the PST program, while the remainder were more sensitive to docetaxel. In the light of the relative equivalence between AC and docetaxel in the advanced setting, our data must be interpreted with caution. In fact, two artifacts impairing the validity of our clinical model cannot be excluded: that AC has a different time to response than docetaxel or that there is a carry-over effect. Both factors substantially impair the reliability of this clinical model. A more appropriate design for such a trial would, thus, have been 4 cycles of AC, then a pause and then 4 of docetaxel. We considered this cleaner study design, but rejected it because of feasibility: all our patients had initially operable disease and ethical constraints did not allow a pause after the first segment of therapy.

The second concern of our study was the low activity of the entire PST program. In fact, although the pCR rate differed marginally from that obtained with regimens of the same duration in a similar patient population and, in particular, from PST with four cycles of AC, (2) recently published trials with longer duration of treatment showed higher rates of pCR.

In a phase II study, six cycles of docetaxel 100 mg/m^2 every three weeks as PST in patients with operable breast cancer produced a global clinical response rate of 68% together with a high pCR rate (19.8 and 35.5% according to the modified Chevallier's and Sataloff's classifications, respectively) (25). The authors found that the tumor shrinkage occurred progressively, with only 40% of complete response obtained after the first four cycles of therapy.

A randomized phase II trial, reported in abstract form (29), evaluated the activity of six cycles of FEC100 (fluorouracil 600 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 600 mg/m^2) or the activity of six cycles of ED (epirubicin 100 mg/m^2, docetaxel 75 mg/m^2) in patients with non-inflammatory, operable T2-T4 tumors. The pCR rate was 24% in both arms.

Preliminary results of another large (358 patients) randomized phase II study in patients with ≥ 3 cm diameter operable tumors indicated that 6 cycles of VE (vinorelbine 25 mg/m^2 days 1,8 and epirubicin 60 mg/m^2 day 1) or 6 cycles of AC at standard doses produced a similar pCR rate of 15% in both arms (30).

Preliminary preoperative results of the NSABP B-27 trial that assigned the patients to receive either four cycles of AC followed by surgery, or four cycles of AC followed by four cycles of docetaxel and then surgery, or four cycles of AC followed by surgery and four cycles of adjuvant docetaxel indicated that the sequential use of docetaxel after AC provided a significantly higher complete clinical response rate (63.6% *vs.* 40.1%, $p<0.001$) and pCR rate (26.1% *vs.* 13.7%) compared to AC only (31).

Similar results were observed in the GEPARDUO trial where the sequence of AC followed by docetaxel (the same regimen as the NSABP B-27 trial) provided a pCR rate of 22.4% (32).

Taken together, these findings suggest two points: that the duration of chemotherapy is crucial in determining the chance of pathological complete remission and that taxanes play a significant role in determining high pCR rates. It is likely that ongoing trials will strengthen and confirm these observations.

Aknowledgements

We wish to thank Dr. Sabrina Guerra for her assistance in reviewing the manuscript.

References

1 Kaufmann M, von Minckwitz G, Smith R, Valero V, Gianni L, Eiermann W, Howell A, Costa SD, Beuzeboc P, Untch M, Blohmer JU, Sinn HP, Sittek R, Souchon R, Tulusan AH, Volm T and Senn H: International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. J Clin Oncol *21*: 2600-2608, 2003.

2 Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, Wickerham DL, Begovic M, DeCillis A, Robidoux A, Margolese RG, Cruz AB Jr, Hoehn JL, Lees AW, Dimitrov NV and Bear HD: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol *16*: 2672-85, 1998.

3 Gianni L, Baselga J, Eiermann W, Porta VG, Semiglazov V, Garcia-Conde J, Zambetti M, Valagussa P and Bonadonna G, for the ECTO Study Group: First report of the European Cooperative Trial in Operable Breast Cancer (ECTO): Effects of primary systemic therapy (PST) on loco-regional disease. Proc Am Soc Clin Oncol *21*: 34a, (Abstract 132), 2002.

4 van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C and Duchateau L: Preoperative chemotherapy in primary operable breast cancer: Results from the European Organization for Research and Treatment of Cancer Trial 10902. J Clin Oncol *19*: 4224-4237, 2001.

5 Jakesz R, for the ABCSG: Comparison of pre- *vs*. postoperative chemotherapy in breast cancer patients: four-year results of Austrian Breast & Colorectal Cancer Study Group (ABCSG) Trial 7. Proc Am Soc Clin Oncol *20*: 32a, (Abstract 125), 2001.

6 Scholl SM, Pierga JY, Asselain B, Beuzeboc P, Dorval T, Garcia-Giralt E, Jouve M, Palangie T, Remvikos Y and Durand JC: Primary *versus* adjuvant chemotherapy in premenopausal patients with tumors considered too large for breast conserving surgery: preliminary results of a randomised trial. Eur J Cancer *30A*: 645-652, 1994.

7 Pohl G, Rudas M, Taucher S, Stranzl T, Steger GG, Jakesz R, Pirker R and Filipits M: Expression of cell cycle regulatory proteins in breast carcinomas before and after preoperative chemotherapy. Breast Cancer Res Treat *78*: 97-103, 2003.

8 Smith IE and Lipton L: Preoperative/neoadjuvant medical therapy for early breast cancer. Lancet Oncology *2*: 561-570, 2001.

9 Faneyte IF, Schrama JG, Peterse JL, Remijnse PL, Rodenhuis S and van de Vijver MJ: Breast cancer response to neoadjuvant chemotherapy: predictive markers and relation with outcome. Br J Cancer *88*: 406-412, 2003.

10 Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, Theriault RL, Singh G, Binkley SM, Sneige N, Buchholz TA, Ross MI, McNeese MD, Buzdar AU, Hortobagyi GN and Singletary SE: Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol *17*: 460-469, 1999.

11 Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, Ah-See AK, Eremin O, Walker LG, Sarkar TK, Eggleton SP and Ogston KN: Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol *20*: 1456-1466, 2002.

12 Nabholtz JM, Senn HJ, Bezwoda WR, Melnychuk D, Deschênes L, Douma J, Vandenberg TA, Rapoport B, Rosso R, Trillet-Lenoir V, Drbal J, Molino A, Nortier JWR, Richel DJ, Nagykalnai T, Siedlecki P, Wilking N, Genot JY, Hupperets PSGJ, Pannuti F, Skarlos D, Tomiak EM, Murawsky M, Alakl M, Riva A and Aapro M, 304 Study Group: Prospective randomized trial of docetaxel *versus* mitomycin C plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. J Clin Oncol *17*: 1413-1424, 1999.

13 Chan S, Friedrichs K, Noel D, Pinter T, Van Belle S, Vorobiof D, Duarte R, Gil Gil M, Bodrogi I, Murray E, Yelle L, von Minckwitz G, Korec S, Simmonds P, Buzzi F, Gonzalez Mancha R, Richardson G, Walpole E, Ronzoni M, Murawsky M, Alakl M and Riva A: Prospective randomized trial of docetaxel *vs* doxorubicin in patients with metastatic breast cancer. J Clin Oncol *17*: 2341-2354, 1999.

14 ten Bokkel Huinink WW, Prove AM, Piccart M, Steward W, Tursz T, Wanders J, Franklin H, Clavel M, Verweij J and Alakl M: A phase II trial with docetaxel (Taxotere) in second line treatment with chemotherapy for advanced breast cancer. Ann Oncol *5*: 527-532, 1994.

15 Ravdin PM, Burris HA 3rd, Cook G, Eisenberg P, Kane M, Bierman WA, Mortimer J, Genevois E and Bellet RE: Phase II trial of docetaxel in advanced anthracycline-resistant or anthracenedione-resistant breast cancer. J Clin Oncol *13*: 2879-2885, 1995.

16 Valero V, Holmes FA, Walters RS, Theriault RL, Esparza L, Fraschini G, Fonseca GA, Bellet RE, Buzdar AU and Hortobagyi GN: Phase II trials of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. J Clin Oncol *13*: 2886-2894, 1995.

17 Nabholtz JM, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Vogel C, Weaver C, Walley B, Martin M, Chap L, Tomiak E, Juhos E, Guevin R, Howell A, Hainsworth J, Fornander T, Blitz S, Gazel S, Loret C and Riva A: Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: interim analysis of the BCIRG 001 study. Proc Am Soc Clin Oncol *21*: 36a, (Abstract 141), 2002.

18 De Laurentiis M: Sequential epirubicin-docetaxel-CMF regimen as adjuvant therapy of early breast cancer: Preliminary results of the Taxit-216 multicenter phase III trial. Proc Am Soc Clin Oncol *22*: 29, (Abstract 115), 2003.

19 Gogas H and Fountzilas G: The role of taxanes as a component of neoadjuvant chemotherapy for breast cancer. Ann Oncol *14*: 667-674, 2003.

20 Hutcheon AW, Heys SD, Sarkar TK, and the Aberdeen Breast Group: Neoadjuvant docetaxel in locally advanced breast cancer. Breast Cancer Res Treat *79(Suppl. 1)*: S19-S24, 2003.

21 Snead DR, Bell JA, Dixon AR, Nicholson RI, Elston CW, Blamey RW and Ellis IO: Methodology of immunohistological detection of oestrogen receptor in human breast carcinoma in formalin-fixed, paraffin-embedded tissue: a comparison with frozen section methodology. Histopathology *23*: 233-8, 1993.

22 Elston CW and Ellis IO: Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology *19*: 403-10, 1991.

23 Buchholz TA, Tucker SL, Masullo L, Kuerer HM, Erwin J, Salas J, Frye D, Strom EA, McNeese MD, Perkins G, Katz A, Singletary SE, Hunt KK, Buzdar AU and Hortobagyi GN: Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. J Clin Oncol *20*: 17-23, 2002.

24 Padhani AR and Ollivier L: The RECIST criteria: implications for diagnostic radiologists. Br J Radiol *74*: 983-986, 2001.

25 Amat S, Bougnoux P, Penault-Llorca F, Fetissof F, Cure H, Kwiatkowski F, Achard JL, Body G, Dauplat J and Chollet P: Neoadjuvant docetaxel for operable breast cancer induces a high pathologic response and breast-conservation rate. Br J Cancer *88*: 1339-1345, 2003.

26 Miller KD, McCaskill-Stevens W, Sisk J, Loesch DM, Monaco F, Seshadri R and Sledge GW Jr: Combination *versus* sequential doxorubicin and docetaxel as primary chemotherapy for breast cancer: a randomized pilot trial of Hoosier Oncology Group. J Clin Oncol *17*: 3033-3037, 1999.

27 Swain SM, Sorace RA, Bagley CS, Danforth DN Jr, Bader J, Wesley MN, Steinberg SM and Lippman ME: Neoadjuvant chemotherapy in the combined modality approach of locally advanced nonmetastatic breast cancer. Cancer Res *47*: 3889-94, 1987.

28 Aapro M: Docetaxel *versus* doxorubicin in patients with metastatic breast cancer who have failed alkylating chemotherapy: a preliminary report of the randomized phase III trial. 303 Study Group. Semin Oncol *25(Suppl 12)*: 7-11, 1998.

29 Luporsi E, Vanlemmens L, Coudert B, Mayer F, Bonneterre J, Petit T, Borel C, Hirsch M and Bey P: 6 cycles of FEC 100 *vs* 6 cycles of Epirubicin-Docetaxel (ED) as neoadjuvant chemotherapy in operable breast cancer patients (Pts): preliminary results of a randomized phase II trial of Girec S01. Proc Am Soc Clin Oncol *19*: 92a, (Abstract 355), 2000.

30 Smith IE, A'Hern R, Coombes G, Hickish T, O'Brien M, Robinson A, Laing R, Hong A, Verrill M and Wardley A, for the TOPIC Trialists Group: A randomised neoadjuvant chemotherapy trial of vinorelbine/epirubicin (VE) *vs* standard doxorubicin/cyclophosphamide (DC) in patients with >3cm diameter operable breast cancer (TOPIC 2). Proc Am Soc Clin Oncol *22*: 21, (Abstract 83), 2003.

31 Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, Margolese R, Theoret H, Soran A, Wickerham DL and Wolmark N: The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary Results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol *21*: 4165-4174, 2003.

32 Von Minckwitz G, Raab G, Schuette M, Hilfrich J, Blohmer JU, Gerber B, Costa SD, Merkle E, Eidtmann H, Lampe W, Jackisch C, duBois A, Caputo A and Kaufmann M: Dose-dense *versus* sequential adriamcycin / docetaxel combination as preoperative chemotherapy (pCHT) in operable breast cancer (T2-3, N0-2,M0) - primary endpoint analysis of the GEPARDUO-Study. Proc Am Soc Clin Oncol *21*: 43a, (Abstract 168), 2002.

Received March 3, 2004
Accepted June 3, 2004