Published in final edited form as:
Breast Cancer Res Treat. 2010 May ; 121(1): 111–120. doi:10.1007/s10549-010-0838-7.

Phase II trial of pegylated liposomal doxorubicin plus docetaxel with and without trastuzumab in metastatic breast cancer: Eastern Cooperative Oncology Group Trial E3198

Antonio C. Wolff,
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans Street, CRB1-189, Baltimore, MD 21231-1000, USA

Molin Wang,
Dana Farber Cancer Institute, Boston, MA, USA

Hailun Li,
Dana Farber Cancer Institute, Boston, MA, USA

Michael R. Pins,
Northwestern University, Chicago, IL, USA

Florence J. Pretorius,
University of Pretoria, Pretoria, South Africa

Kendrith M. Rowland,
Carle Clinic, Urbana, IL, USA

Joseph A. Sparano, and
Montefiore-Einstein Cancer Center, Albert Einstein College of Medicine, Bronx, NY, USA

Nancy E. Davidson
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans Street, CRB1-189, Baltimore, MD 21231-1000, USA

Antonio C. Wolff: awolff@jhmi.edu

Abstract

The purpose of this trial was to determine cardiac toxicity and overall efficacy of the pegylated liposome doxorubicin (PLD)–docetaxel couplet alone if HER2-negative metastatic breast cancer (internal control) or with trastuzumab if HER2-positive disease. Upon central HER2 confirmation, 84 eligible patients received induction with PLD (30 mg/m^2) and docetaxel (60 mg/m^2) every 3 weeks (maximum eight cycles), alone if HER2-negative (arm A; $N = 38$) or plus trastuzumab (4 mg/kg once, then 2 mg/kg weekly) if HER2-positive disease (arm B; $N = 46$) as first-line therapy. Maintenance therapy (without PLD) allowed. Primary objectives were to determine whether congestive heart failure (CHF) rate >3% and the efficacy/toxicity of each arm. CHF rate was <3% in each arm. Response rate, median progression-free-, and overall survival in arms A and B were 47.4 and 45.7%, 11 and 10.6 months, and 24.6 and 31.8 months, respectively. Trastuzumab arm

Correspondence to: Antonio C. Wolff, awolff@jhmi.edu.

*Present Address:*M. R. Pins, Advocate Lutheran General Hospital, Chicago, IL, USA
Present Address: N. E. Davidson, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA

The study was conducted on behalf of the Eastern Cooperative Oncology Group.

Presented in part at the 2003 American Society of Clinical Oncology annual meeting and the 2004 San Antonio Breast Cancer Symposium.

was associated with higher rates of hand foot syndrome (grade 3: 22 vs. 38%; $P = 0.16$; overall 51 vs. 75%, $P = 0.03$) and treatment discontinuation due to toxicity/patient withdrawal (13 vs. 28%; $P = 0.11$). Febrile neutropenia occurred in ~10% of patients. In conclusion, concurrent administration of trastuzumab with PLD–docetaxel was not associated with higher risk of cardiac toxicity compared with PLD–docetaxel alone, but led to excessive hand-foot syndrome.

Keywords

Pegylated liposomal doxorubicin; Trastuzumab; Docetaxel; Metastatic breast cancer; Cardiotoxicity

Introduction

The anthracyclines (i.e., doxorubicin, epirubicin) and the taxanes (i.e., paclitaxel, docetaxel) are the most active cytotoxic agents for the treatment of metastatic breast cancer. A pooled analysis of randomized trials conducted in the pre-taxane era demonstrated that doxorubicin-containing regimens resulted in a higher response rate and improved survival in patients with metastatic breast cancer [1]. More recently, the taxanes have proven to be effective agents for patients with metastatic breast cancer who have progressive disease after doxorubicin-containing therapy [2, 3] or when used as first-line therapy [4–6]. Given their antitumor activity, differing mechanism of action, and partially non-overlapping toxicity profiles, several groups have evaluated doxorubicin–taxane combinations. Several phase III trials in metastatic breast cancer demonstrated improved response rate and time to disease progression for doxorubicin–taxane combinations compared with doxorubicin-containing regimens without taxanes or taxanes alone, although cardiotoxicity was problematic for some combinations [7]. In addition, although combination of trastuzumab with conventional anthracyclines in HER2-positive disease is more effective than chemotherapy alone, the combination produces prohibitive cardiotoxicity [8].

Liposomes are closed vesicular structures which envelope water soluble molecules that were initially described in the 1960's [9]. They may serve as a vehicle for delivering cytotoxic agents more specifically to tumor and by limiting exposure of normal tissues to the drug. A pegylated form of liposomal doxorubicin is approved for the treatment of ovarian carcinoma, Kaposi's sarcoma, and multiple myeloma (in combination with bortezomib), and is known to have an improved cardiac safety profile compared with conventional anthracycline preparations [10, 11]. pegylated liposome doxorubicin (PLD) has been shown to preferentially localize in tumor tissue in a variety of animal models, including a mouse mammary carcinoma [12], and some clinical studies in humans have shown better tumor localization and penetration in Kaposi's sarcoma [13], malignant effusions [14], and metastatic bone lesions from breast cancer [15] (as reviewed in reference [16]). Two phase III trials have compared single agent PLD (50 mg/m^2 every 4 weeks) with doxorubicin (60 mg/m^2) as first-line therapy [17] or with vinorelbine (or mitomycin-C/5-fluorouracil) as second or greater line therapy for metastatic breast cancer [18]. The former study found PLD to be as effective and less cardiotoxic than doxorubicin, and the latter found PLD to have comparable efficacy to vinorelbine.

Based upon these considerations, we had previously performed a phase I–II trial of PLD plus docetaxel in 41 patients with advanced breast cancer [19]. We reported that the recommended phase II dose of the combination was 30 mg/m^2 of PLD and 60 mg/m^2 of docetaxel given every 3 weeks, and observed objective response in 16 of 31 patients (52%, 95% CI 34–70%) with metastatic disease and median time to tumor progression of 8 months. In the current trial that forms the basis for this report, we sought to determine the

safety and efficacy of the PLD–docetaxel regimen used alone in HER2-negative disease or in combination with trastuzumab in HER2-positive disease. The primary objectives were to determine if the incidence of congestive heart failure (CHF) for either arm exceeded 3%, and the efficacy of the combinations as reflected by the response rate, response duration, progression-free survival, and overall survival. Several phase I–II studies have tested the combination of non pegylated [20] and pegylated liposomal doxorubicin regimens in combination with trastuzumab [21–23]. To our knowledge, ECOG 3198 is the only trial with an appropriate internal cardiac safety control arm (patients with HER2-negative disease not treated with trastuzumab).

Patients and methods

Patient eligibility

Patients were required to have histologically confirmed adenocarcinoma of the breast with evidence of metastatic progression, measurable and/or evaluable disease, no prior chemotherapy for metastatic disease, no prior adjuvant anthracycline therapy, no prior radiotherapy (other than to the conserved breast, to the post-mastectomy chest wall, or to a limited field involving ≤25% of marrow-containing bone), an ECOG performance status of 0 to 2, age>18 years, and adequate organ function within 4 weeks prior to registration, including renal (serum creatinine ≤ 1.5 mg/dl), hematologic (granulocytes ≥ 1,500/mm^3 and platelets ≥ 100,000/mm^3), hepatocellular (SGOT ≤ 2.5 × the upper limit of normal and bilirubin within normal limits for institution), and cardiac function (left ventricular ejection fraction [LVEF] at or above the lower institutional limits of normal as assessed by MUGA scan or echocardiogram obtained within 6 weeks prior to registration). Exclusion criteria included a history of myocardial infarction, CHF, or arrhythmia requiring medication, history of hypertension or systolic or diastolic dysfunction, or EKG evidence of ventricular hypertrophy, conduction abnormality, or serious arrhythmia within 4 weeks of registration, history of deep venous thrombosis, pulmonary thromboembolism, or other thromboembolic condition, untreated brain metastases, brain metastases undergoing radiation or brain metastasis as the sole site of disease, or prior non-breast invasive malignancies within 5 years (with the exception of curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix).

Registration and central HER2 testing

After signed informed consent was obtained, patients were pre-registered and had a representative tumor sample from the primary tumor or metastatic disease sent to the ECOG Pathology Coordinating Office for determination of HER2 expression status by the DAKO HerceptTest® (Dako A/S, Glostrup, Denmark). HER2-positive status was defined as IHC 3+, or 2+ score if evidence of gene amplification (HER2:CEP17 ration ≥ 2.0) using the PathVysion® assay (Abbott Molecular Inc, Des Plaines, IL) [24].

Treatment plan

All patients received PLD 30 mg/m^2 IV followed by docetaxel 60 mg/m^2 IV, 1 h after PLD completion, every 3 weeks for a total of eight cycles, either alone in patients with HER2-negative disease (arm A) or in combination with trastuzumab (arm B) in HER2-positive disease (Fig. 1). Patients with stable or responding disease following the first eight cycles of induction chemotherapy could receive optional maintenance chemotherapy with single-agent docetaxel (weekly [30 mg/m^2] or every 3 weeks [75 mg/m^2]). All patients with HER2-positive disease continued to receive weekly trastuzumab (2 mg/kg IV weekly). Patients in both arms received pyridoxine 200 mg PO daily as prophylaxis against hand-foot syndrome [25, 26].

Cardiac monitoring

All patients had baseline assessment of LVEF performed by echocardiogram or nuclear scan within 6 weeks of registration, after cycle 4, after cycle 8, and 3 months after PLD was discontinued (with the same method used to evaluate LVEF each time). Clinical CHF was defined as having at least two of the following features in addition to a decrease in LVEF: S3 gallop, basilar rales, dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea, and/or cardiomegaly on chest X-ray. All protocol treatments were to be stopped if the LVEF decreased by ≥20% from baseline value, if the LVEF decreased by ≥10% from baseline value and is below the lower institutional limits of normal, or if the LVEF decreased by ≥5% below the lower institutional limits of normal. These definitions were consistent with previous ECOG trials [27, 28].

Statistical considerations

In the original design, 42 eligible patients (46 total patients) were to be entered in each arm. Assuming a CHF rate of up to 3% as being an acceptable degree of toxicity, observing 4 or more patients with CHF within either group would be considered excessive. There would be a 4% chance of observing CHF in 4 or more of 42 eligible patients if the true rate of CHF was 3% and an 89% chance if the true rate was 15%. The design gave 88% power to detect a 9% difference in absolute change after cycle 4 or 8 from baseline between the two arms. A two-stage design was employed in the HER2-positive group (arm B). After 24 patients were entered, accrual was to be suspended until data on the post cycle 4 LVEF evaluations were obtained; this arm was to be reopened if no significant absolute drop in LVEF was observed (<4% on average).

The Wilcoxon two-sample test was used to test for differences in LVEF decrease from baseline and in cumulative doses of PLD and docetaxel between the two arms. The Wilcoxon signed rank test was used to test whether the LVEF decrease from baseline was different from zero. Fisher's exact test was used to compare the frequencies of toxicity between arms. Two-sided *P* values were reported. Exact binomial confidence intervals were used to describe response rates. The method of Kaplan and Meier was used to characterize duration of response, progression-free survival, and overall survival.

Results

Patient characteristics

Eighty-nine patients were accrued between October 19, 2000, and September 7, 2004, of whom 84 were eligible, including 38 eligible patients in arm A and 46 eligible patients in arm B (Fig. 1). Reasons for ineligibility included no baseline electrocardiogram (ECG) within 4 weeks of registration ($N = 3$), baseline ECG showed left ventricular hypertrophy ($N = 1$), and hypertension requiring beta-blocker therapy ($N = 1$). Eighty-four patients were eligible (Table 1). For the entire population, the median age was 53 years (range 23–80 years), 93% had an ECOG performance status of 0 or 1, 58% had at least three disease sites, and 20% patients received prior adjuvant chemotherapy. Patients with HER2-negative disease had a higher incidence of symptomatic disease as evidenced by an ECOG PS of 1–2 (55.2 vs. 36.9%), but had a lower incidence ER/PR-negative disease (31.6 vs. 45.5%).

Treatment information

A total of 251 induction cycles were given in arm A, of which 217 (87%) were given without dose adjustment and or interruption; the median number of cycles given was 8 (range 1–8). A total of 273 induction cycles were given in arm B, of which 201 (74%) were given without dose adjustment and or interruption; the median number of cycles given was 7 (range 2–8). During induction therapy, patients on arms A and B received a median of 199.9

mg/m^2 (range 29.9–246.2) and 169.8 mg/m^2 (range 29.8–253.1) of PLD, and a median of 435.4 mg/m^2 (range 59.9–489.8) and 360.7 mg/m^2 (range 59.6–506.8) of docetaxel, respectively. Although patients in the trastuzumab arm received 15% less PLD and 17% less docetaxel in median dose, the differences in the cumulative doses were not significantly different between the two arms for either PLD ($P = 0.12$) or docetaxel ($P = 0.12$).

All eight induction cycles were administered to 71% of patients in arm A and 48% in Arm B, respectively. Patients who went off treatment before cycle 8 received a median of four cycles of therapy in both arms (ranges 1–6 and 2–7, respectively). While comparing arms A and B, more patients in arm B discontinued induction therapy due to disease progression (10.5 vs. 19.6%), toxicity (13.2 vs. 21.7%), and patient withdrawal (0 vs. 6.5%). Fourteen patients (37%) on arm A and 20 (43%) on arm B began maintenance therapy and received a median of five docetaxel cycles (range 1–40) and 16 trastuzumab ± docetaxel cycles (range 3–65), respectively (one cycle = 3 weeks of therapy).

Cardiac toxicity

Accrual to arm B was temporarily suspended between April 23, 2002, and November 6, 2002, for a planned cardiac toxicity analysis; the study was reopened after the analysis met prespecified safety criteria. There was no difference in the incidence of grade 1–3 cardiac events in either arm (24.4 vs. 25%; $P = 0.99$). Only one patient in arm A developed clinically defined CHF, which occurred 3 weeks after cycle 4, and was accompanied by an 11% drop in LVEF from baseline (64–53%). Information regarding LVEF data obtained at baseline, after cycle 4, after cycle 8, and 30 or more days after cycle 8 is described (Table 2). The average absolute decrease in LVEF from baseline for arms A and B were 2.3 and 1.6% after cycle 4, 4.2 and 4.9% after cycle 8, and 0.9 and 6.2% at 30 or more days (median, 2.7 months; range 1.6–16.3 months) after cycle 8. There was no statistically significant difference between the decrease in the two arms after cycle 4 ($P = 0.79$), after cycle 8 ($P = 0.68$), or 30 or more days after cycle 8 ($P = 0.07$). The trend for a greater difference in LVEF after cycle 8 was due to recovery of cardiac function in arm A compared with a plateau in cardiac function in arm B (Fig. 2).

Response rate, response duration, progression-free survival, and overall survival

Median follow-up was 47.2 months for arm A and 48.4 months for arm B. The overall response rates (including complete and partial responses) were 47.4% (95% CI 31.0–64.2%) in arm A and 45.7% (95% CI 30.9–61.0%) in arm B, including one complete response in arm A (2.6%) and four complete responses in arm B (8.7%). The median duration of response was 10.1 months (95% CI 6.7–15.4 months) and 14.7 months (95% CI 7.8–23.7 months), median PFS was 11 months (95% CI 8.6–12.8 months) and 10.6 months (95% CI 5.6–15.7 months) (Fig. 3a), and median overall survival was 24.6 months (95% CI 14.7–37.3 months) and 31.8 months (95% CI 23.7–44.9 months) (Fig. 3b), respectively. Three-year survival rates were 35.9% (95% CI 20.5–51.4%) and 47.6% (95% CI 33.2–62.1%) and 5-year survival were 24.9% (95% CI 9.6–40.3%) and 22.2% (95% CI 1.9–42.6%), respectively.

Overall toxicity

The incidence of worst grade toxicities for all treated patients is summarized (Table 3). One patient in arm A who had a baseline ECOG performance status of 2 died on day 7 of the first cycle with infection associated with grade 4 neutropenia. The eligibility criteria were subsequently modified to allow only ECOG performance status 0 or 1, and no subsequent treatment associated deaths occurred. In comparing arms A and B, the most common grades 3 and 4 toxicities occurring in at least 10% of patients included neutropenia (59 vs. 67%),

leukopenia (54 vs. 58%), hand foot reaction (22 vs. 38%), infection (17 vs. 25%), stomatitis (17 vs. 23%), anemia (12 vs. 12%), febrile neutropenia (12 vs. 10%), fatigue (5 vs. 17%), and dehydration (2 vs. 10%), indicating generally more toxicity in the trastuzumab arm. When considering all grades, the trastuzumab arm was associated with significantly higher rate of hand foot syndrome (51 vs. 75%; $P = 0.03$), and a higher rate of discontinuation of induction therapy due to toxicity and/or patient withdrawal (13.2 vs. 28.3%; $P = 0.11$).

Discussion

We performed a phase II trial of pegylated liposomal doxorubicin (30 mg/m^2) plus docetaxel (60 mg/m^2) every 3 weeks for up to eight treatment cycles in patients with metastatic breast cancer, used alone in HER2-negative disease or in combination with trastuzumab in HER2-positive disease. The rate of CHF was less than 3% in both arms, including the trastuzumab arm, indicating that the primary study endpoint (cardiac safety) was met. The objective response rate was approximately 45%, and median progression-free survival was approximately 11 months for both the HER2-negative and HER2-positive groups in our trial. Another trial that reported on the efficacy and safety of PLD (50 mg/m2 every 4 weeks) in combination with trastuzumab for HER2-positive metastatic cancer demonstrated comparable efficacy, a 30% rate of grade 3 hand-foot syndrome and no significant cardiotoxicity, which is very consistent with our findings [22].

In a previous trial performed by the ECOG (E1193), 739 patients with metastatic breast cancer who had no prior adjuvant doxorubicin or prior chemotherapy for metastatic disease were randomized to receive doxorubicin (60 mg/m^2), paclitaxel (175 mg/m^2/24 h infusion), or the combination (50 and 150 mg/m^2/24 h plus granulocyte colony-stimulating factor) as first-line therapy [5]. The response rates were 36, 34, and 47%, respectively, and median time to treatment failure was 5.8, 6, and 8 months, respectively (the definition of treatment failure corresponded to the progression-free survival endpoint used in this study). Although the difference favoring the combination was statistically significant for both end points, it was associated with more toxicity and did not improve median overall survival (18.9 vs. 22.2 vs. 22 months, respectively). Likewise, the PLD–docetaxel doublet evaluated in this trial in a similar patient population appears to be more effective when compared with other studies evaluating PLD alone (30% response and 6.9 month median PFS [17]) or docetaxel alone (47% response rate and 6.1 month median time to progression [29]) when used as first-line therapy.

Similar findings were confirmed in a subsequent phase III trial comparing the identical PLD–docetaxel doublet evaluated in our trial with single agent docetaxel (75 mg/m^2) in 751 patients with metastatic breast cancer [30]. However, in contrast to our trial, which required no prior anthracycline exposure and central HER2 testing (which directed the use of concurrent trastuzumab), the subsequent phase III trial required relapse at least one or more years after prior adjuvant anthracycline therapy, did not include HER2 testing for all patients, nor include concurrent trastuzumab for known HER2-positive tumors. In that study, the PLD–docetaxel combination was associated with significantly improved median PFS (9.5 vs. 6.9 months, HR = 0.66, 95% CI 0.56–0.78; $P = 0.000001$) and ORR (35 vs. 26%; $P = 0.0085$), but no difference in median overall survival (20.5 vs. 20.6 months, HR = 1.02, 95% CI 0.86–1.22; $P = 0.81$). Moreover, there was no difference in the incidence of grade ≥2 symptomatic cardiac events in the two arms (5 vs. 4%) or CHF (1% in both arms), providing unequivocal evidence of cardiac safety in patients who had prior adjuvant anthracycline exposure (median prior cumulative doxorubicin dose of 240 mg/m^2). On the other hand, the PLD–docetaxel combination was associated with higher rates of other toxicities, including grades 3 and 4 HFS (24 vs. 0%) and stomatitis (12 vs. 1%). Those higher rates of certain toxicities did not translate into differences in self reported patients

outcomes as measured by the FACT-B instrument, which were similar in the two treatment arms. The results of our study, therefore, provide complementary information to the subsequent phase III trial, demonstrating similar toxicity profile and comparable efficacy for the PLD–docetaxel combination in patients with no prior anthracycline therapy confirmed to have HER2-negative tumors.

Other studies have also evaluated the cytotoxic doublet therapy compared with single agent cytotoxic therapy in patients with HER2-positive disease treated concurrently with trastuzumab. Robert et al. compared trastuzumab plus paclitaxel (175 mg/m2) with the same regimen plus carboplatin (AUC 6) every 3 weeks for six cycles; the addition of carboplatin produced a higher response rate (52 vs. 36%; $P = 0.04$) and median PFS (10.7 vs. 7.1 months; $P = 0.03$), but not overall survival (median 35.7 vs. 32.2 months) [31]. Pegram et al. reported that when compared to trastuzumab plus docetaxel (100 mg/m2), the combination of trastuzumab plus docetaxel (75 mg/m2) and carboplatin (AUC 6) every 3 weeks for eight cycles was not associated with improved response rate (73% in both arms) or median time to disease progression (11.1 vs. 10.4 months; $P = 0.57$) [32]. Therefore, it is uncertain whether the addition of carboplatin to a taxane with trastuzumab offers a clinical benefit in HER2-positive disease, and this may depend on the taxane component of the doublet.

In our E3198 trial, the three-drug regimen of PLD–docetaxel plus trastuzumab was associated with excessive HFS despite the prophylactic use of high-dose pyridoxine, which had been shown to prevent HFS in a canine model [26]. On the other hand, there was no increase in the risk of cardiac toxicity in the HER2-positive group (treated with trastuzumab) compared with the HER2-negative group (which did not receive trastuzumab), thereby serving as an internal control arm, a unique feature of our trial design. The cardiac safety profile observed in our trial (primary endpoint) confirms a previous report demonstrating the efficacy and cardiac safety trastuzumab plus PLD [22].

The findings of the subsequent phase III trial comparing the PLD–docetaxel combination with docetaxel mono-therapy are consistent with many other studies comparing combination versus single agent cytotoxic therapy, demonstrating improved response and PFS without an impact on survival and more toxicity [33]. Overall survival is generally not improved in such trials in part due to the availability of multiple agents that have activity when used as second or greater line therapy [34]. Based upon these consistent observations, it is generally recommended that cytotoxic therapy be given as single agents sequentially rather than in combination [34]. However, there are circumstances in which doublet cytotoxic therapy may be indicated and appropriate, such as patients with advanced, visceral disease, or substantial tumor-associated symptoms that require more rapid and effective palliation.

In conclusion, we found that the PLD–docetaxel combination to be an effective regimen for patients with metastatic breast cancer, whether used alone in HER2-negative disease or in combination with trastuzumab in HER2-positive disease. Of great interest, the addition of trast-uzumab to the doublet did not result in an increase in the risk of cardiac toxicity (study primary endpoint) but was associated with a higher risk of hand-foot syndrome. The results of our study provide complementary information to other trials demonstrating that PLD is in effective alternative to other cytotoxic agents for metastatic breast cancer, including doxorubicin as first-line therapy [17], or vinorelbine as second or greater line therapy [18].

Acknowledgments

We acknowledge the support from Ortho Biotech Products, L.P., for the provision of investigational drug and financial support for central HER2 testing and from Genentech, Inc., for the provision of investigational drugs. We are also grateful to Dako A/S and Abbott Molecular for their support with free assay kits for central HER2 testing, and to Adekunle Raji, Susan Edgerton, and other members of the ECOG Pathology Coordinating Office. This work

was supported in part by grants from the Department of Health and Human Services and the National Institutes of Health CA23318 to the ECOG statistical center, CA66636 to the ECOG data management center, CA21115 to the ECOG coordinating center and chairman's office, CA16116 to The Johns Hopkins Kimmel Cancer Center, CA59307 to the University of Pretoria, CA13650 to the Mayo Clinic (Carle Clinic), and CA14958 to the Albert Einstein College of Medicine.

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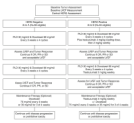

Fig. 1.
Study schema.
Note: All patients also received pyridoxine 200-mg PO daily continuously while on PLD

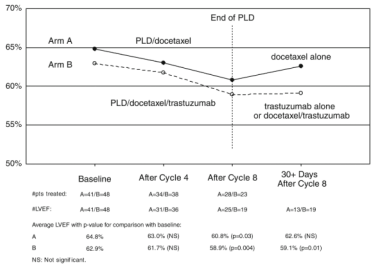

Fig. 2.
Mean LVEF values in all treated patients in both arms A and B

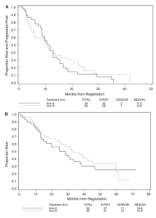

Fig. 3.
Progression-free survival (**a**) and overall survival (**b**) in all eligible patients

Table 1

Patient characteristics (eligible patients)

	Arm A HER2-negative (*N* = 38)	Arm B HER2-positive (*N* = 46)	Total (*N* = 84)
Age			
Median	53	53	53
Range	33–80	23–80	23–80
Race			
White	28 (73.7%)	33 (71.7%)	61 (72.6%)
Hispanic	3 (7.9%)	5 (10.9%)	8 (9.5%)
Black	4 (10.5%)	5 (10.9%)	9 (10.7%)
Other	3 (7.9%)	3 (6.5%)	6 (7.1%)
Performance status			
0	17 (44.7%)	29 (63.0%)	46 (54.8%)
1	17 (44.7%)	15 (32.6%)	15 (38.1%)
2	4 (10.5%)	2 (4.3%)	2 (7.1%)
Site of disease			
Lung	15 (39.5%)	23 (50.0%)	38 (45.2%)
Bone	20 (52.6%)	18 (39.1%)	38 (45.2%)
Liver	20 (52.6%)	20 (43.5%)	40 (47.6%)
≥3 disease sites involved	19 (50.0%)	30 (65.2%)	49 (58.3%)
Menopausal status			
Pre	10 (26.3%)	15 (32.6%)	25 (29.8%)
Post	13 (34.2%)	15 (32.6%)	28 (33.3%)
Not specified, age < 50	6 (15.8%)	3 (6.5%)	9 (10.7%)
Not specified, age ≥50	9 (23.7%)	13 (28.3%)	22 (26.2%)
ER/PgR status			
ER−/PgR−	12 (31.6%)	21 (45.7%)	33 (39.3%)
ER+ and/or PgR+	22 (57.9%)	22 (47.8%)	44 (52.4%)
Unknown	4 (10.5%)	3 (6.5%)	7 (8.3%)
Prior adjuvant chemotherapy	9 (23.7%)	8 (17.4%)	17 (20.2%)
Prior systemic therapy containing taxane	1 (2.6%)	0 (0%)	1 (1.2%)
Prior radiation therapy			
Adjuvant only	8 (21.1%)	2 (4.3%)	10 (11.9%)
Advanced only	4 (10.5%)	4 (8.7%)	8 (9.5%)
Both	2 (5.3%)	1 (2.2%)	3 (3.6%)
Prior hormonal therapy			
Adjuvant Only	6 (15.8%)	5 (10.9%)	11 (13.1%)
Advanced Only	6 (15.8%)	2 (4.3%)	8 (9.5%)
Both	4 (10.5%)	3 (6.5%)	7 (8.3%)
Prior surgery (with therapeutic intent)			
Adjuvant only	17 (44.7%)	18 (39.1%)	35 (41.7%)
Advanced only	2 (5.3%)	3 (6.5%)	5 (6.0%)

	Arm A HER2-negative (*N* = 38)	Arm B HER2-positive (*N* = 46)	Total (*N* = 84)
Both	2 (5.3%)	2 (4.3%)	4 (4.8%)

Table 2

LVEF data for all treated patients

LVEF values (%)	Arm A (*N* = 41)			Arm B (*N* = 48)			Wilcoxon two-sample test
	N	Mean	(SD)	*N*	Mean	(SD)	
Baseline	41	64.8	(8.3)	48	62.9	(7.2)	
Post cycle 4	31	63.0	(7.9)	36	61.7	(7.2)	
Post cycle 8	25	60.8	(8.2)	19	58.9	(7.4)	
≥30 days after cycle 8	13	62.6	(6.4)	19	59.1	(7.5)	
Baseline minus post cycle 4	31	2.3	(7.5)	36	1.6	(8.0)	*P* = 0.79
Baseline minus post cycle 8	25	4.2	(8.8)	19	4.9	(6.7)	*P* = 0.68
Baseline minus ≥30 days after cycle 8	13	0.9	(7.1)	19	6.2	(9.4)	*P* = 0.07

Table 3

Grades 3 and 4 toxicities occurring in least 5% of all treated patients

	Arm A (*N* = 41)				Arm B (*N* = 48)			
	Grade				Grade			
	1,2	3	4	5	1,2	3	4	5
Cardiovascular and/or pulmonary								
Dyspnea	9 (22%)	2 (5%)	1 (2%)	–	6 (13%)	2 (4%)	–	–
Thrombosis/embolism	–	3 (7%)	1 (2%)	–	–	–	–	–
Constitutional								
Fatigue	27 (66%)	2 (5%)	–	–	27 (56%)	7 (15%)	1 (2%)	–
Cutaneous								
Dry eye	4 (10%)	–	–	–	3 (6%)	–	–	–
Tearing	13 (32%)	2 (5%)	–	–	15 (31%)	–	–	–
Ocular other	2 (5%)		–	–	4 (8%)	–	–	–
Hand-foot reaction	12 (29%)	9 (22%)	–	–	18 (38%)	18 (38%)	–	–
Nail changes	17 (41%)	–	–	–	18 (38%)	–	–	–
Pigmentation	4 (10%)	–	–	–	5 (10%)	–	–	–
Rash/desquamation	6 (15%)	–	–	–	12 (25%)	1 (2%)	–	–
Gastrointestinal								
Dehydration	–	1 (2%)	–	–	3 (6%)	5 (10%)	–	–
Nausea	21 (51%)	1 (2%)	–	–	28 (58%)	3 (6%)	–	–
Stomatitis	26 (63%)	7 (17%)	–	–	29 (60%)	11 (23%)	–	–
Diarrhea w/o prior colostomy	11 (27%)	2 (5%)	–	–	21 (44%)	1 (2%)	–	–
Hematologic								
Hemoglobin	27 (66%)	5 (12%)	–	–	33 (69%)	5 (10%)	1 (2%)	–
Leukocytes	13 (32%)	15 (37%)	7 (17%)	–	15 (31%)	26 (54%)	2 (4%)	–
Neutrophils	7 (17%)	4 (10%)	20 (49%)	–	9 (19%)	7 (15%)	25 (52%)	–
Platelets	9 (22%)	2 (5%)	–	–	6 (13%)	1 (2%)	–	–
Infection								
Febrile neutropenia	–	4 (10%)	1 (2%)	–	–	4 (8%)	1 (2%)	–
Infection	5 (12%)	7 (17%)	–	1 (2%)	13 (27%)	11 (23%)	1 (2%)	–

	Arm A (*N* = 41)				Arm B (*N* = 48)			
	Grade				Grade			
	1,2	3	4	5	1,2	3	4	5
Neurologic								
Neuropathy motor	2 (5%)	–	–	–	6 (13%)	3 (6%)	–	–
Renal								
Creatinine	2 (5%)	–	2 (5%)	–	2 (4%)	1 (2%)	1 (2%)	–
Worst degree all toxicities	7 (17%)	12 (29%)	21 (51%)	1 (2%)	6 (13%)	14 (29%)	28 (58%)	0

Note: Toxicities shown in this table include all toxicities in which grades 3 and 4 events occurred in at least 5% of patients (with all grades shown) in each group and cutaneous toxicities of all grades