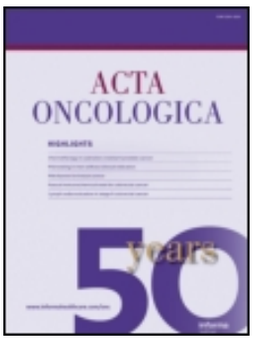

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

Phase II study of neoadjuvant pegylated liposomal doxorubicin and cyclophosphamide ± trastuzumab followed by docetaxel in locally advanced breast cancer

Malgorzata K. Tuxen, Soeren Cold, Ulla B. Tange, Eva Balslev & Dorte L. Nielsen

To cite this article: Malgorzata K. Tuxen, Soeren Cold, Ulla B. Tange, Eva Balslev & Dorte L. Nielsen (2014) Phase II study of neoadjuvant pegylated liposomal doxorubicin and cyclophosphamide ± trastuzumab followed by docetaxel in locally advanced breast cancer, Acta Oncologica, 53:10, 1440-1445, DOI: 10.3109/0284186X.2014.921727

To link to this article: https://doi.org/10.3109/0284186X.2014.921727

Phase II study of neoadjuvant pegylated liposomal doxorubicin and cyclophosphamide ± trastuzumab followed by docetaxel in locally advanced breast cancer

MALGORZATA K. TUXEN[1], SOEREN COLD[2], ULLA B. TANGE[3], EVA BALSLEV[4] & DORTE L. NIELSEN[1]

[1]*Department of Oncology, Herlev University Hospital, Herlev, Denmark,* [2]*Department of Oncology, Odense University Hospital, Odense, Denmark,* [3]*Department of Oncology, Rigshospitalet, Copenhagen, Denmark and* [4]*Department of Pathology, Herlev University Hospital, Herlev, Denmark*

To the Editor,

Neoadjuvant chemotherapy (NAC) plays an important role in patients with locally advanced breast cancer (LABC). Achievement of pathologic complete response (pCR) at surgery is a surrogate measure of disease-free and overall survival (OS), both in LABC and operable breast cancer [1–3]. Unfortunately, achievement of pCR in patients with LABC is rare, and there is still a need to improve the outcome of the treatment.

Anthracycline-based and taxanes-based therapies are among the most active regimens in the treatment of breast cancer, also frequently used as NAC. Combination chemotherapy with anthracyclines and taxanes, given concurrently or sequentially for at least six cycles or six months, respectively, is currently considered to be the standard neoadjuvant treatment [4]. However, the best schedule for administrating of these drugs has not been identified.

The clinical utility of anthracyclines is limited by their potential risk to cause cumulative cardiac damage. Pegylated liposomal doxorubicin (PLD) has been developed in order to improve the therapeutic index of conventional anthracyclines and studies have shown a significantly reduced risk of cardiotoxicity compared with doxorubicin. O'Brien et al. [5] conducted a phase III study with 509 metastatic breast cancer patients, comparing doxorubicin with PLD in first-line treatment. The study demonstrated that the overall risk of cardiotoxicity was significantly higher with doxorubicin than PLD [hazard ratio (HR) = 3.16; 95% confidence interval (CI) 1.58–6.31; $p < 0.001$]. At the same time, both agents had comparable activity with similar OS of 22 and 21 months for doxorubicin and PLD, respectively, (HR = 0.94, 95% CI 0.74–1.19).

We decided in this phase II trial to replace classical anthracycline by PLD in an attempt to

Correspondence: M. K. Tuxen, Department of Oncology, Herlev University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark. Tel: +45 38682750. Fax: +45 38683507. E-mail: gosia.tuxen@regionh.dk

(Received 11 October 2013; accepted 28 April 2014)

ISSN 0284-186X print/ISSN 1651-226X online © 2014 Informa Healthcare
DOI: 10.3109/0284186X.2014.921727

increase the feasibility of the treatment and to offer a safe combination with trastuzumab for patients with HER2 positive LABC. The primary end-point of this study was the clinical response rate (RR) of neoadjuvant PLD (Caelyx®) and cyclophosphamide ± trastuzumab followed by docetaxel in patients with LABC. Secondary end-points included determination of pCR rate and evaluation of the safety of the combination regimen.

Material and methods

Eligibility criteria

Patients with inflammatory, LABC or large operable breast cancer (tumor >5 cm) were enrolled in a Danish phase II neoadjuvant trial PO050903.

Eligibility criteria were as follows: female, age 18–75 years and Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; histologically proven primary breast cancer $T_{3\text{-}4}$, N_X, M_0 or T_X, $N_{2\text{-}3}$, M_0; adequate bone marrow, hepatic and renal function confirmed by a prestudy examination; left ventricular ejection fraction (LVEF) $>50\%$ by MUGA scan for HER2 positive breast cancer; expected lifetime of more than three months; absence of significant cardiac disease [$\leq$ New York Heart Association (NYHA) class II]; measurable primary tumor or lymph nodes or non-measurable disease (inflammatory breast cancer) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Patients were excluded if they had any other severe or uncontrolled systemic disease, if they received experimental treatment less than 30 days before the study entry, or if they had a previous history of another malignant disease (other than non-melanoma skin cancer or in situ cervix uteri) less than five years before the study entry. Patients with psychological, familiar, social or geographic conditions that could influence on their compliance were also excluded.

Adequate contraception and a negative pregnancy test were required for women of child-bearing potential. Pregnant patients and those breast-feeding were excluded.

Signed informed consent was obtained from all patients prior to the study.

The study was approved by the local Ethical Committee and each institutional review board. The study was registered in clinicaltrials.gov (NCTO1206881) and was conducted in compliance with Good Clinical Practices.

Treatment

Patients received four cycles of PLD (Caelyx®) 35 mg/m^2 and cyclophosphamide 600 mg/m^2, both administered intravenously on day 1 every 21 days followed by four cycles of docetaxel 100 mg/m^2 administered intravenously on day 1 every 21 days. Patients with HER2-positive tumors were concurrently treated with trastuzumab $8 \rightarrow 6$ mg/kg administered intravenously on day 1 every 21 days for eight cycles. All patients received granulocyte-colony stimulation factor (G-CSF) after each cycle of docetaxel.

After the completion of NAC, patients underwent surgery either mastectomy or breast conserving surgery. Axillary lymph node dissection was performed in all patients, except patients with previous negative sentinel lymph node biopsy.

Postoperative, adjuvant treatment was given according to Danish Breast Cancer Cooperative (DBCG) guidelines.

Study assessments

Tumor assessments were performed by physical examination at baseline and day 1 of each chemotherapy cycle and by mammography with ultrasound or MR scan of the breast at baseline and every 2nd cycles. RECIST version 1.1. were applied to evaluate clinical response.

pCR was defined as no histological evidence of invasive cancer in the breast. pCRT was defined as no histological evidence of invasive cancer in the breast and axillary lymph nodes.

Adverse events were obtained at baseline and after each chemotherapy cycle. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2 (NCI-CTC, v2). Cardiac toxicity was assessed using MUGA scan at baseline and every second cycle of trastuzumab.

All tumors were examined for ER, PGR and HER2. ER and PGR were determined by immunohistochemistry (IHC) and HER2 by IHC or by fluorescence in situ hybridization (FISH). Tumors were considered as ER-positive if more than 10% of cancer cells demonstrated positive staining by IHC. Patients were classified as having HER2-positive tumors when tumors were scored as 3 + by IHC, or if gene amplification (>2.0) was identified by FISH.

Statistical analysis

The sample size was calculated by the two-stage Simon's optimal design for phase II studies [6].

Results

Patient population

From March 2009 to October 2010, 49 patients with inflammatory, LABC or large operable breast cancer (tumor >5 cm) were enrolled. One patient was

excluded from the study as she turned out to have sarcoma. Thus, 48 patients were assessable. The characteristics of the eligible patients are shown in Table I.

Study treatments

All eight cycles of NAC were completed as planned in 40 patients (83%). Six patients (13%) discontinued treatment due to toxicity after 5–7 cycles and two discontinued due to patient's wish and clinical suspicion of progression, respectively. The patient, who was clinically suspected for progression, was operated after seven cycles of chemotherapy. However, the operation showed partial response.

One patient developed an anaphylactic reaction to the first infusion of PLD and received afterwards eight cycles of cyclophosphamide and docetaxel. The patient was therefore excluded from response and safety evaluation.

Efficacy

Totally, 47 patients were assessable for response evaluation (Table II). Three of 47 patients (6%) showed no sign of residual tumor after NAC on preoperative clinical examination and mammography with ultrasound (or MR scan of the breast). Overall, 39 patients (83%) demonstrated a clinical response.

Table I. Patient demographics and disease characteristics (48 patients).

Characteristic	Number (%)
Median age, years (range)	50 (31–69)
ECOG performance status	
0	47 (98)
1	1 (2)
Menopausal status	
Premenopausal	26 (54)
Postmenopausal	22 (46)
Median tumor size, cm (range)	7 (2–15)
T-classification	
T2	2 (4)
T3	32 (67)
T4	14 (29)
N-classification	
N0	14 (29)
N1	30 (63)
N2	3 (6)
N3	1 (2)
Histology	
Ductal carcinoma	29 (60)
Lobular carcinoma	11 (23)
Other	8 (17)
Inflammatory	9 (19)
ER status	
Positive	38 (79)
Negative	10 (21)
HER2 status	
Positive	11 (23)
Negative	37 (77)
Triple negative	7 (15)

Table II. Investigator-assessed clinical and pathological response rate (47 patients).

Response rate	Number (%)
Complete response (CR)	3 (6)
Partial response (PR)	36 (77)
Objective response rate (CR+PR)	39 (83)
Stable disease	7 (15)
Progressive disease	1 (2)*
Pathological complete response (pCR)	9 (19)
Total pathological complete response (pCRT)	6 (13)

*The patient was clinically suspected for progression but showed response at surgery.

Patients were operated 3–4 weeks after the last cycle of NAC. Breast conserving surgery was performed in six patients (13%) and mastectomy in 41 patients (87%).

Histological examination of surgical specimens demonstrated pCR in nine patients (19%, 95% CI 9.2–33.3%) and pCRT in six patients (13%, 95% CI 4.8–25.7%). Three of nine patients with pCR (33%) had triple negative tumor, three patients (33%) HER2 negative, ER positive tumor, one patient (11%) HER2 positive, ER positive tumor and two patients (22%) HER2 positive, ER negative tumor. In this small patient population of 47 patients, three of seven patients (43%) with triple negative tumors and three of 10 patients (30%) with HER2 positive tumors achieved pCR.

Safety

The incidence of grade 3–4 toxicity is reported in Supplementary Table I available online at http://informahealthcare.com/doi/abs/10. 3109/0284186X.2014.921727. The primary toxicity observed was skin toxicity, which was manageable. Palmar-plantar erythrodysesthesia (PPE) grade 3 was experienced in 10 patients (21%) and grade 4 in six patients (13%), respectively. As expected, PPE was observed during treatment with PLD. However, some of the patients experienced significant worsening of symptoms after change of chemotherapy to docetaxel (Supplementary Figure I available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.921727).

Most of other side effects were due to the treatment with docetaxel. Beside PPE, no patients experienced other grade 4 toxicity during treatment with PLD and cyclophosphamide and only five patients (11%) suffered toxicity grade 3 related to this combination: five patients (11%) grade 3 fatigue and one of those patients (2%) also grade 3 mucositis. As expected, pain (myalgia and arthralgia) and neurotoxicity was only described in connection with docetaxel.

The main cause of hospitalization was febrile neutropenia in nine patients (19%). However, only one patient developed febrile neutropenia during treatment with PLD and cyclophosphamide. The remaining eight patients experienced this side effect in association with docetaxel. All patients recovered quickly after treatment with antibiotics. There were no treatment-related deaths.

Six patients (13%) discontinued treatment due to toxicity, but only two patients due to side effects, grade 4 PPE, to PLD. All six patients received a total of 5–7 cycles, and in all patients a clinical response was obtained.

One patient experienced an anaphylactic reaction to the first infusion of PLD and received afterwards eight cycles of cyclophosphamide and docetaxel in combination with trastuzumab. Surgery after NAC demonstrated pCR.

Cardiac toxicity was assessed in patients with HER2 positive breast cancer using MUGA scan. Maintained normal LVEF was seen throughout the study in all patients.

ER and HER2 status before and after NAC

Nine of 47 patients had pCR at the time of operation. Thus, 38 tissue specimens were sufficient for ER and HER2 evaluation both before and after NAC.

ER changed from positive to negative in one patient (2%).

HER2 expression changed in six patients (13%), from negative to positive in five patients (11%) and from positive to negative in one patient (2%).

Discussion

Several previous studies have reported clinical RRs following NAC of between 58% and 91%, with a reported pCR of 3–41% [7–21] (Supplementary Table II available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.921727). These studies were mostly performed in patients with different tumor stages, operable breast cancer as well as locally advanced disease, making it difficult to compare tumor response for patients with LABC alone. In this phase II study, a combination of PLD and cyclophosphamide ± trastuzumab followed by docetaxel has shown an overall clinical response of 83% and pCR of 19%, respectively. The rate of pCR reached in the current study was relatively high in view of large tumor size (median 7 cm) in most of the patients. Generally, the efficacy reported was comparable with results of other trials in LABC [7–21].

Published reports of neoadjuvant trials suggested that pCR is frequently observed in a subset of tumors, e.g. HER2-positive and ER negative tumors [22]. In our study pCR was achieved in nine patients (19%). The small sample size does not allow any conclusions. We observed, however, that 43% with triple negative tumors and 30% with HER2 positive tumors achieved pCR.

There is no consensus regarding the optimal schedule for treatment of LABC. However, there is agreement that anthracyclines and taxanes are the reference drugs, and different combinations of these drugs have been examined in a number of phases II and III trials [7–21]. PLD offers an alternative to conventional antracyclines for treatment of patients with breast cancer. To our knowledge there are only a few studies testing PLD in combination with other antineoplastic drugs in the neoadjuvant setting in patients with LABC [14–17]. Different drug combinations used in these studies produced 62–74% overall RR and 3–16% pCR rate. In all these studies, PLD was well tolerated and toxicity was generally mild.

PLD rarely produces nausea and vomiting or significant alopecia. The most significant side effect is skin toxicity. Although 16 patients (34%) developed grade 3–4 PPE in our study, this side effect was manageable and in all cases reversible. Changes were mostly seen after third or fourth cycle of PLD and cyclophosphamide, possibly due to a cumulative effect of PLD. Some of the patients experienced significant worsening of symptoms after a change of chemotherapy to docetaxel, indicating overlapping effect of skin toxicities between PLD and docetaxel.

Mucositis is another well-known side effect to PLD. However, in our cohort of patients only one patient (2%) experienced grade 3 mucositis during treatment with PLD. PLD in combination with cyclophosphamide was generally well tolerated and other grade 3 toxicities were uncommon.

Nine patients (19%) required hospital admission due to febrile neutropenia, only one patient during treatment with PLD and eight during treatment with docetaxel. Overall, 87% of patients completed the full schedule in the present study, which demonstrates the feasibility and safety of this drug combination.

HER2-positive breast cancer is associated with aggressive disease and poor prognosis. Trastuzumab given with chemotherapy improves the outcome of patients with metastatic [23] and early, operable breast cancer [24]. This therapeutic approach has also been evaluated in the neoadjuvant setting [21,25]. The addition of trastuzumab to NAC led to large increase in the pCR rate. Concomitant treatment of trastuzumab and anthracyclines is, however, associated with highly increased risk of

cardiotoxicity [26] and this regimen is still controversial. The use of less cardiotoxic anthracyclines can minimize the risk of cardiac side effects. Previous trials using concurrent administration of PLD and trastuzumab showed a safe cardiac profile of this combination [27]. In the current study, patients with HER2 positive disease received careful cardiac monitoring and no changes in cardiac function were seen.

Breast cancer is a heterogeneous disease and treatment is based on the disease status and pathological features. Studies comparing samples from primary tumor with corresponding relapsed tumor have demonstrated discordances in ER, PR and HER2 status [28–30]. The rate of discordance ranged between approximately 10% and 30% and included both "gains" and "losses" of receptor expression. The knowledge about influence of NAC in LABC on expression of molecular markers is limited. In this study, ER decreased in one patient (2%). HER2 expression changed in six patients (13%), from negative to positive in five patients (11%) and from positive to negative in one patient (2%), suggesting that HER2 status should be re-evaluated on surgical tissue specimens after NAC in order to select optimal adjuvant treatment.

In conclusion, the present study is relatively small with the heterogeneous patient population and the results have to be interpreted with some caution. However, this study indicates that the combination of PLD and cyclophosphamide ± trastuzumab followed by docetaxel is highly active in LABC with an acceptable safety profile. The primary toxicity was cutaneous toxicity which was manageable. In addition, this study suggests that concurrent administration of PLD with trastuzumab in patients with HER2 positive breast cancer might offer an efficacious anthracycline-based regimen without the known associated cardiotoxicity of conventional anthracyclines plus trastuzumab.

Acknowledgments

Study conduct was partially funded by a grant from Schering-Plough. Schering-Plough did not contribute to analysis and interpretation of data, to the writing or submitting of the manuscript.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Von Minckwitz G, Kaufmann M, Kuemmel S, Fasching PA, Eiermann W, Blohmer JU, et al., for the GBG and AGO-B Study Groups. Correlation of various pathologic complete response (pCR) definitions with long-term outcome and the prognostic value of pCR in various breast cancer subtypes: Results from the German neoadjuvant meta-analysis. J Clin Oncol 2011;29(Suppl):1028.

[2] Montagna E, Bagnardi V, Rotmensz N, Viale G, Pruneri G, Veronesi P, et al. Pathologic complete response after preoperative systemic therapy and outcome: Relevance of clinical and biologic baseline features. Breast Cancer Res Treat 2010;124:689–99.

[3] Bear HD, Anderson S, Smith RE, Geyer CE Jr, Mamounas EP, Fisher B, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project protocol B-27. J Clin Oncol 2006;24:2019–27.

[4] Kaufmann M, von Minckwitz G, Mamounas EP, Cameron D, Carey LA, Cristofanilli M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012;19:1508–16.

[5] O'Brian MER, Wiger N, Inbar M, Rosso R, Grischke E, Santoro A, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCI (CAELYX™ /Doxil®) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004;15:440–9.

[6] Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trial 1989;10:1–10.

[7] Buzdar AU, Singletary SE, Theriault RL, Booser DJ, Valero V, Ibrahim N, et al. Prospective evaluation of paclitaxel versus combination chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. J Clin Oncol 1999;17:3412–7.

[8] Miller KD, McCaskill-Stevens W, Sisk J, Loesch DM, Monaco F, Seshadri R, et al. Combination versus sequential doxorubicin and docetaxel as primary chemotherapy for breast cancer: A randomized pilot trial of the Hoosier Oncology Group. J Clin Oncol 1999;17:3033–7.

[9] Bujanda DA, Sarmiento UB, Suarez MAC, Ruiz MP, Gonzalez MAL, Morales JA. Epirubicin, cyclophosphamide and weekly paclitaxel as neoadjuvant chemotherapy for stage II and III breast cancer. J Cancer Res Clin Oncol 2006;132:332–8.

[10] Evans TR, Yellowlees A, Foster E, Earl H, Cameron DA, Hutcheon AW, et al. Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: An Anglo-Celtic Cooperative Oncology Group study. J Clin Oncol 2005;23:2988–95.

[11] Kelly H, Kimmick G, Dees EC, Collichio F, Gatti L, Sawyer L, et al. Response and cardiac toxicity of trastuzumab given in conjunction with weekly paclitaxel after doxorubicin/ cyclophosphamide. Clin Breast Cancer 2006;7:237–43.

[12] Rocca A, Peruzzotti G, Ghisini R, Viale G, Veronesi P, Luini A, et al. A randomized phase II trial comparing preoperative plus perioperative chemotherapy with preoperative chemotherapy in patients with locally advanced breast cancer. Anticancer Drugs 2006;17:1201–9.

[13] Tiezzi DG, Andrade JM, Ribeiro-Silva A, Zola FE, Marana HR, Tiezzi MG. HER-2, p53, p21 and hormonal receptors proteins expression as predictive factors of response and prognosis in locally advanced breast cancer treated with neoadjuvant docetaxel plus epirubicin combination. BMC Cancer 2007;7:36.

[14] Gogas H, Papadimitriou C, Kalofonos HP, Bafaloukos D, Fountzilas G, Tsavdaridis D, et al. Neoadjuvant chemotherapy with a combination of pegylated liposomal doxorubicin (Caelyx) and paclitaxel in locally advanced breast cancer: A phase II study by the Hellenic Cooperative Oncology Group. Ann Oncol 2002;13:1737–42.

[15] Rossi D, Baldelli AM, Casadei V, Fedeli SL, Alessandroni P, Catalano V, et al. Neoadjuvant chemotherapy with low dose of pegylated liposomal doxorubicin plus weekly paclitaxel in operable and locally advanced breast cancer. Anticancer Drugs 2008;19:733–7.

[16] Artioli G, Mocellin S, Borgato L, Cappetta A, Bozza F, Zavagno G, et al. Phase II study of neoadjuvant gemcitabine, pegylated liposomal doxorubicin, and docetaxel in locally advanced breast cancer. Anticancer Res 2010;30: 3817–21.

[17] Dellapasqua S, Mazza M, Rosa D, Ghisini R, Scarano E, Torrisi R, et al. Pegylated liposomal doxorubicin in combination with low-dose metronomic cyclophosphamide as preoperative treatment for patients with locally advanced breast cancer. Breast 2011;20:319–23.

[18] Taguchi T, Masuda N, Nakayama T, Motomura K, Tsukamoto F, Shimazu K, et al. Phase II trial in Japan of sequential administration of weekly paclitaxel followed by FEC as neoadjuvant chemotherapy for locally advanced breast cancer (KBCSG0206 trial: Kinki Breast Cancer Study Group (KBCSG)). Oncology 2010;78:302–8.

[19] Therasse P, Mauriac L, Welnicka-Jaskiewicz M, Bruning P, Cufer T, Bonnefoi H, et al. Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: An EORTC-NCIC-SAKK multicenter study. J Clin Oncol 2003;21: 843–50.

[20] Gianni L, Semiglazov V, Manikhas GM, Eiermann W, Lluch A, Tjulandin S, et al. Neoadjuvant trastuzumab in locally advanced breast cancer (NOAH): Antitumour and safety analysis. J Clin Oncol 2007;25(Suppl):532 (abstract)

[21] Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): A randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010;375:377–84.

[22] Berrutoni A, Brizzi MP, Generali D, Ardine M, Dogliotti L, Bruzzi P, et al. Presurgical systemic treatment of nonmetastatic breast cancer: Facts and open questions. Oncologist 2008; 13:1137–48.

[23] 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;344:783–92.

[24] 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;353:1673–84.

[25] Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005;23:3676–85.

[26] Bowles EJA, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: A retrospective cohort study. J Nat Cancer Inst 2012;104:1293–305.

[27] Chia S, Clemons M, Martin LA, Rodgers A, Gelmon K, Pond GR, et al. Pegylated liposomal doxorubicin and trastuzumab in HER-2 overexpressing metastatic breast cancer: A multicentre phase II trial. J Clin Oncol 2006; 24:2773–8.

[28] Liedtke C, Broglio K, Moulder S, Hsu L, Kau SW, Symmans WF, et al. Prognostic impact of discordance between triple-receptor measurements in primary and recurrent breast cancer. Ann Oncol 2009;20:1953–8.

[29] Lindström L, Karlsson E, Wilking UM, Johansson U, Hartman J, Lidbrink EK, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are instable throughout tumor progression. J Clin Oncol 2012;30: 2601–8.

[30] Curigliano G, Bagnardi V, Viale G, Fumagalli L, Rotmensz N, Aurillo G, et al. Should liver metastases of breast cancer be biopsied to improve treatment choice? Ann Oncol 2011;22:2227–33.

Supplementary material available online

Supplementary Tables I, II and Figure 1 available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.921727.