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ORIGINAL ARTICLE

High efficacy of pre-operative trastuzumab combined with paclitaxel following doxorubicin & cyclophosphamide in operable breast cancer

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Abstract

Background. Trastuzumab in combination with adjuvant chemotherapy improves disease free survival and overall survival in HER2 over-expressing breast cancer patients. Data concerning the use of trastuzumab in the neo-adjuvant setting is limited. We aimed to compare outcome of HER2 over-expressing breast cancer patients treated with either standard chemotherapy, consisting of doxorubicin, cyclophosphamide and a taxane to outcome of patients treated with the same chemotherapy regimen with the addition of trastuzumab in concurrence with paclitaxel. *Methods.* We conducted a retrospective review of all consecutive HER2 over-expressing breast cancer patients treated at the participating institutions during the study period and received neo-adjuvant therapy. Allocation to trastuzumab was not based on clinical parameters and was approved only by part of the insurers. Clinical and pathological characteristics, as well as response rate and type of surgery were analyzed. *Results.* Thirty seven patients received chemotherapy alone and 24 patients received chemotherapy and trastuzumab. A similar distribution of age, clinical stage and histology was noted in both groups. The rate of pathological complete response (pCR) was significantly higher among the trastuzumab-treated group compared to chemotherapy-alone group (75 vs. 24% respectively, $p = 0.0002$). pCR in the breast was noted in 18 of 24 (75%) compared to 10 of 36 (28%, $p = 0.0005$) and pCR in the axillary lymph nodes was noted in 19 of 20 (95%) compared to 8 of 28 (29%, $p = 0.0001$), in the trastuzumab group compared to the chemotherapy-alone group respectively. The safety profile was similar between both groups and no clinical cardiotoxicity were noted. *Conclusions.* The addition of trastuzumab to standard chemotherapy in the neo-adjuvant setting improves pathological complete response rates in HER2 over-expressing breast cancer patients.

Neo-adjuvant systemic therapy is an accepted standard approach for women with early breast cancer and has been shown to reduce tumor size and allow for breast conserving surgery [1]. While pre-operative therapy does not prolong disease free or overall survival compared to post-operative therapy, it can provide predictive and prognostic information and may also provide *in vivo* assessment of tumor sensitivity to therapy [2,3]. Thus, pathological complete response (pCR), which can be achieved in up to 35% of the patients treated by anthracycline or taxane based pre-operative therapy, is associated with improved survival [3–5]. Complete pathological response in the axillary lymph nodes has also been demonstrated to be an independent predictor of long-term outcome, regardless of the response in the breast tissue [5,6].

The HER2 gene is a member of the epidermal-growth factor receptor family, which controls cell growth, differentiation and survival [7]. HER2 over-expression occurs in up to 25% of invasive breast cancers and is associated with an aggressive disease pattern and poor outcome [8,9]. HER2 is the target of the monoclonal antibody trastuzumab, which has been shown to improve outcome in both the metastatic and adjuvant settings [10–13]. Several large phase III trials have demonstrated a significant improvement of disease free and overall survival

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following the addition of trastuzumab to various adjuvant chemotherapy regimens [12–15]. To date, the use of pre-operative trastuzumab has been described in a limited number of relatively small studies [16–22]. In a single published randomized trial, which evaluated the pre-operative use of trastuzumab following paclitaxel and fluorouracil/epirubucin/cycolphosphamide (FEC), pCR was noted in 66.7% of the 23 patients assigned to chemotherapy and trastuzumab, compared to only 25% of the 19 patients assigned to chemotherapy alone [16]. Significantly lower pCR rates were reported in other studies [17–22]. However, as these trials lacked a comparative control arm and none of them incorporated both a taxane and an anthracycline in the pre-operative regimen, the interpretation of their results is limited.

In Israel, prior to the general reimbursement of trastuzumab for the treatment of early breast cancer, the drug was available only by some of the insurers. During that period of time, all HER2 over-expressing patients who were allocated for neo-adjuvant chemotherapy at the participating institutions, were treated by a regimen containing doxorubicin and cyclophosphamide (AC) followed by a taxane, but only some of these patients were also treated by trastuzumab. As treatment allocation was not directly associated with clinical parameters, we had a unique opportunity to compare two similar groups of patients allocated to neo-adjuvant treatment consisting of chemotherapy alone or chemotherapy plus trastuzumab.

Patients and methods

Study population and pre-treatment evaluation

The study population included all consecutive operable breast cancer patients with HER2/neu over-expression who underwent neo-adjuvant therapy at three institutions: Sheba Medical Centre (42 patients), Rambam Hospital (12 patients) and Assaf Harofeh Hospital (7 patients) between June 2002 and December 2005. Patients' charts were reviewed and clinical data, including stage at diagnosis, age, ethnicity, genetics and menopausal status were documented. Stage was defined according to the 2002 American Joint Committee on Cancer Staging System for Breast Cancer [24].

All patients underwent radiological evaluation of both breasts by mammography and ultra-sonography. Axillary lymph nodes were assessed by ultra-sonography. Patients with clinically negative axillary nodes underwent sentinel node sampling and those with suspicious nodes on imaging underwent nodal sampling prior to commencement of therapy. Biopsy was not mandatory for patients with pathological nodes on both examination and imaging.

Pre-treatment pathology reports were reviewed for tumor histology, size, lymph nodes involvement, and grade. Hormone receptor (HR) status was determined by immuno-histochemistry (IHC) staining. HR-positive status was defined by presence of $>10\%$ positive cells for the estrogen receptor (ER) or the progesterone receptors (PR). HER2 status was confirmed by either 3+ on IHC analysis (range 0–3+), (Ventana, Pathway HER 2 clone CB II), or a positive result of greater than 2.0 on fluorescence in situ hybridization (FISH) for HER2 amplification (pathvision kit -Vysis). FISH studies were performed on all IHC 2+ cases.

Left ventricular ejection fraction (LVEF) was evaluated by either MUGA or echocardiogram and only patients with a LVEF $\geq 50\%$ were allocated to this protocol. Trastuzumab treated patients had further assessment of LVEF at the conclusion of therapy.

Neo-adjuvant therapy

All patients received four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every three weeks, followed by either a weekly taxane (paclitaxel or docetaxel) together with weekly trastuzumab (4 mg/kg initial loading dose followed by 2 mg/kg) for 12 weeks or only a taxane (weekly or every three weeks). After surgery all women received radiotherapy as per unit protocol. Those who received trastuzumab completed one year of therapy (6 mg/kg three-weekly). Hormone positive patients received adjuvant hormonal therapy.

Treatment assessment

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, Version 2.0. Breast imaging was conducted either immediately prior to or following the final course of treatment. Clinical and radiological complete response was defined as no evidence of tumor on clinical examination or imaging. Clinical and radiological partial response was defined as at least a 50% decrease in the diameter of a lesion.

All patients underwent surgery within 6 weeks of completion of neo-adjuvant therapy. Pathology reports were evaluated and pCR was defined as the absence of invasive disease in both the breast and the axillary lymph nodes.

Data and statistical analysis

The distribution of all categorical variables by study group was tabulated. Fisher exact tests were used for

the analysis of categorical data and student t-test was used for continuous variables. All p-values reported were two-sided; values ≤ 0.05 were considered to be statistically significant.

Results

Patient characteristics

Sixty-one HER2-overexpressing breast cancer patients were allocated to neo-adjuvant treatment during the study period. HER2 expression score, as determined by IHC, was 3+ in 58 patients, and 2+ in three patients. In these three patients, HER2 positivity was confirmed by FISH.

Thirty-seven of the patients received chemotherapy only and 24 received chemotherapy plus trastuzumab. Those that received trastuzumab completed one year of therapy (6mg/kg three-weekly) following surgery. The mean patients' age was 49, and similar distribution of age and menopausal status was noted in both groups (Table I). At presentation clinical stage T2-3 was noted in 65 and 80% of the patients in the chemotherapy alone and the chemotherapy plus trastuzumab group respectively, and more patients in the chemotherapy alone group presented with T4 disease (24 vs. 4% respectively, $p = 0.19$ for T stage distribution, Table I). Similar distribution of nodal involvement was noted, with 76 and 83% node positive status in the chemotherapy alone group and the chemotherapy plus trastuzumab group, respectively ($p = 0.4$, Table I). More patients in the chemotherapy alone group had HR positive tumors, compared to the chemotherapy plus trastuzumab group (65 vs. 37% respectively, $p = 0.05$, Table I). Invasive duct carcinoma histology was noted in 92% of both study groups.

Response to therapy

Clinical CR, as determined by physical examination of the breast and axilla, was observed in 19 (79%) patients in the chemotherapy plus trastuzumab group, compared to 12 (32%) of the patients in chemotherapy alone group ($p = 0.0006$, Table II). pCR rate, in both the breast and lymph nodes, was also significantly higher in the chemotherapy plus trastuzumab group compared to chemotherapy alone (75 vs. 24% respectively, $p = 0.0002$, Table II). A further analysis was made comparing the pCR rate only in patients with clinically Tx-T3 tumors – statistical significance was maintained with a pCR of 78 vs. 25%, $p < 0.0001$, favoring the trastuzumab group (data not shown).

In light of the prognostic significance attributed to a pCR in the axillary lymph nodes [7,8], analysis of pCR was performed by site, either in the breast tissue or axilla. pCR in the breast was noted in 75% of the chemotherapy plus trastuzumab group compared to 28% in the chemotherapy alone group ($p = 0.0005$), while axillary pCR was noted in 95% of the chemotherapy plus trastuzumab group compared to 29% in the chemotherapy alone group ($p = 0.0005$, Table II).

All patients underwent surgery at the conclusion of neo-adjuvant therapy. No differences were noted

Table I. Distribution of patients' characteristics at diagnosis.

	Chemotherapy alone (N = 37)	Chemotherapy plus trastuzumab (N = 24)	Overall P
Mean age (range, years)	49 (29-68)	49 (29-66)	0.5
Menopausal Status (N,%)			
Pre-menopausal	18 (49)	12 (50)	0.41
Post-menopausal	19 (51)	12 (50)	
Histology (N,%)			
IDC*	34 (92)	22 (92)	0.9
Other	3 (8)	2 (8)	
Clinical T stage (N,%)			
Tx	1 (3)	2 (8)	0.19
T1	3 (8)	2 (8)	
T2	10 (27)	11 (46)	
T3	14 (38)	8 (34)	
T4	9 (24)	1 (4)	
Clinical Nodal (N,%)			0.4
Node negative	9 (24)	4 (17)	
Node positive	28 (76)	20 (83)	
HR** Status (N,%)			0.05
Positive	24 (65)	9 (37)	
Negative	13 (35)	15 (63)	

*IDC: Invasive duct carcinoma; **HR: hormone receptor.

Table II. Response to therapy.

	Chemotherapy Alone (N,%)	Chemotherapy and Trastuzumab (N,%)	Overall P
cCR*	12 (32)	19 (79)	0.0006
pCR†	9 (24)	18 (75)	0.0002
pCR in breast	10/36†† (28)	18 (75)	0.0005
pCR in lymph nodes**	8/28 (29)	19/20 (95)	0.0001
Breast conserving surgery	25 (68)	18 (75)	0.38

* cCR, clinical complete response; † pCR, pathological complete response; †† calculated per number of patients with clinically T1-4 pre-treatment; **calculated per number of patients with pre-treatment biopsy proven positive lymph nodes pre-treatment.

in the type of the surgery performed in both groups, with 75% having underwent lumpectomy in the chemotherapy plus trastuzumab group compared to 68% in the chemotherapy alone group ($p = 0.38$, Table II).

No statistically significant association was noted between HR status and response (data not shown).

Toxicity

There were no treatment related deaths. The incidence of grade 3 and 4 hematological and non-hematological toxicity was similar in both groups. No patients developed symptomatic (grade 3 and 4) heart failure in either group. Five patients in the trastuzumab group had more than a 10% reduction in LVEF by the conclusion of therapy. However, in only one patient was the LVEF below 55% by the end of treatment, with an LVEF of 53% (Table III).

Discussion

We report high clinical and pathological response rates following the addition of trastuzumab to a standard chemotherapy regimen consisting of both an anthracycline and a taxane. To our knowledge, only seven groups reported on the efficacy of neo-adjuvant trastuzumab therapy. All these studies were relatively small, all but one were non-randomized single arm studies, and none of them incorporated standard chemotherapy protocols used in daily clinical practice (Table IV). Thus, although retrospective, our study is unique for the inclusion of a control group and for the use of a standard chemotherapy regimen.

Table III. Adverse events (total number of incidents in study).

	Chemotherapy Alone N = 37	Chemotherapy and Trastuzumab N = 24
Treatment delays	2	2
Dose reductions	1	3
Protocol adjustments	5	0
Incidents of grade 3-4 Non-hematologic toxicity	7	8
Incidents of grade 3-4 hematologic toxicity	3	4
Incidents of febrile neutropenia	3	3
Mean pre-trastuzumab LVEF	N/A	64%
Mean post-trastuzumab LVEF	N/A	63%
LVEF reduction of $\geq 10\%$ (N,%)	N/A	5 (21)
LVEF reduction to $<50\%$	0	0
Symptomatic congestive heart failure	0	0

Although the studies differ considerably in patients' population, chemotherapy regimen used and the length of trastuzumab therapy, several conclusions may be drawn from the comparison between them. The highest response rates were reported by us and by Buzdar et al. [16,23]. A major difference between these two studies and all other studies is the use of both an anthracycline and a taxane together with trastuzumab. This combination has been reported to be highly active in the adjuvant setting [13,15] and our data suggest it as the preferable regimen in the neo-adjuvant setting as well. As pCR following neo-adjuvant treatment is associated with a better prognosis [1,2], perhaps the use of this combination, which is associated with the highest pCR, could also be associated with improved long-term outcome. Long-term follow-up is needed in order to elucidate whether the high pCR will indeed translate into a survival benefit. Lower pCR (38%) were reported recently in a preliminary analysis of the use of trastuzumab with an anthracycline and a taxane containing chemotherapy regimen in 228 HER2-over-expressing breast cancer patients. However, while our patients were all operable at diagnosis, all patients in this study had locally advanced breast cancer, manifested as either T4, N2 or inflammatory breast cancer [25]. The difference in breast conserving rates was not significantly different between the two groups and indeed reflects the inclusion of a significant proportion of patients with early operable breast cancer.

The optimal length of trastuzumab therapy in the neo-adjuvant setting has not been determined, and the published trials report on use ranging from four

Table IV. Summary of published trials of pre-operative trastuzumab.

	Inclusion criteria (staging)	Pre-operative Treatment	Week on Trastuzumab	Number of patients	pCR
Current study	I-IIIB	AC-T	–	37	24%
		AC-T-H	12	24	75%
Buzdar et al. [16]	II-IIIA	T-FEC	–	19	25%
		T-FEC-H	24	23	67%
Burstein et al. [17]	II-III	TH	12	40	18%
Limentani et al. [18]	IIB-IIIB	DV-H	12	31	39%
Gennari et al. [19]	II-IIIA	H	4	11	9%
Coudert et al. [20]	II-IIIA	DH	18	33	47%
Hurley et al. [21]	III	DP-H	12	48	23%
Coudert et al. [22]	II-IIIA	DC-H	18	72	39%

Abbreviations: T, paclitaxel; FEC, fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; DV, docetaxel, navelbine; DH, docetaxel, trastuzmab, DP, docetaxel, cisplatin; DC, docetaxel, carboplatin; pCR, pathological complete response; N/A, not applicable.

to 24 weeks (Table IV). Our data may suggest that 12 weeks of trastuzumab treatment, when administered following an anthracycline and concomitantly with a taxane may be sufficient to achieve maximal response rates.

Unique to our study is the high proportion of patients who underwent lymph node sampling prior to commencement of therapy. Thus, in contrast to previous studies [16–22], in which only clinically positive or suspicious lymph nodes were sampled, our study provides a more accurate assessment of axillary nodal status. We noted a very high rate of axillary pCR (95%). As axillary pCR is considered to be a very strong prognostic factor, our findings further emphasize the importance of incorporating trastuzumab into neo-adjuvant treatment in HER2 over-expressing breast cancer patients [5,6].

As reported in large phase III studies [12–15], the addition of trastuzumab to chemotherapy was safe and the toxicity profile of chemotherapy plus trastuzumab was comparative to chemotherapy alone both in terms of hematological and cardiac toxicities.

It is important to note that a potential source of bias is the manner by which patients obtained the trastuzumab. As mentioned earlier, at the time of our study trastuzumab was not yet reimbursed by all insurers and therefore the drug was only administered to those who could either afford to purchase the drug, had appropriate insurance coverage or whom were able to obtain funding for the drug via charitable funds established for the specific purpose of providing financial aid in purchasing new and expensive biological agents. While certainly socio-economic differences may exist between women who had or did not have private insurance, women from all socio-economic means could apply for assistance from the charitable fund. It is also important to note that in Israel hormone-replacement therapy was readily available from all health providers thus minimizing concern about the potential biological impact of different levels of insurance.

While this study is retrospective, patients' allocation was independent of clinical features and treatment regimens were uniform. Indeed, the two groups were well balanced for both patient and tumor characteristics. As trastuzumab is now considered the standard of care in HER2-over expressing breast cancer, it is unlikely that any further prospective randomized study, comparing the efficacy of chemotherapy alone to chemotherapy plus trastuzumab will ever be conducted. Indeed, the only published phase III study was terminated early following efficacy analysis after only 23 patients were treated with trastuzumab [16, Table IV]. Thus, our study provides important comparative data regarding the efficacy of trastuzumab in the neo-adjuvant setting.

In conclusion, the addition of 12 weeks of neo-adjuvant trastuzumab to a standard chemotherapy regimen containing both an anthracycline and a taxane is safe and highly active, and should be an integral part of neo-adjuvant treatment in operable HER2-over-expressing breast cancer patients.

References

[1] Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: An update. J Clin Oncol 2006;24:1940–9.

[2] Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672–85.

[3] Ellis P, Smith I, Ashley S, Walsh G, Ebbs S, Baum M, et al. Clinical prognostic and predictive factors for primary chemotherapy in operable breast cancer. J Clin Oncol 1998;16:107–14.

[4] Kuerer HM, Newman LA, Buzdar AU, Hunt KK, Dhingra K, Buchholz TA, et al. Residual metastatic axillary lymph nodes following neoadjuvant chemotherapy predict disease-free survival in patients with locally advanced breast cancer. Am J Surg 1998;176:502–9.

[5] Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol 2005;23:9304–11.

[6] Rouzier R, Extra JM, Klijanienko J, Falcou MC, Asselain B, Vincent-Salomon A, et al. Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. J Clin Oncol 2002;20:1304–10.

[7] Yarden Y, Sliwkowski M. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001;2:127–37.

[8] Burstein J. The distinctive nature of HER2-positive breast cancers. N Engl J Med 2005;353:1652–4.

[9] Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177–82.

[10] Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719–26.

[11] 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 over expresses HER2. N Engl J Med 2001;344:783–92.

[12] Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659–72.

[13] 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;353:1973–84.

[14] Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809–20.

[15] Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Pawlicki M, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→T) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. Breast Cancer Res Treat 2005;94(suppl 1):S5.

[16] Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathologic complete remission rate after pre-operative 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.

[17] Burstein HJ, Harris LN, Gelman R, Lester SC, Nunes RA, Kaelin CM, et al. Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: A pilot study. J Clin Oncol 2003;21:46–53.

[18] Limentani SA, Brufsky AM, Erban JK, Jahanzeb M, Lewis D. Phase II study of pre-operative docetaxel, vinorelbine, and trastuzumab followed by surgery and adjuvant doxorubicin plus cyclophosphamide in women with human epidermal growth factor receptor 2-overexpressing locally advanced breast cancer. J Clin Oncol 2007;25:1232–8.

[19] Gennari R, Menard S, Fagnoni F, Ponchio L, Scelsi M, Tagliabue E, et al. Pilot study of the mechanism of action of preoperative trastuzumab in patients with primary operable breast tumors overexpressing HER2. Clin Cancer Res 2004;10:5650–5.

[20] Coudert BP, Arnould L, Moreau L, Chollet P, Weber B, Vanlemmens L, et al. Pre-operative systemic (neo-adjuvant) therapy with trastuzumab and docetaxel for HER2-overexpressing stage II or III breast cancer: Results of a multicenter phase II trial. Ann Oncol 2006;17:409–14.

[21] Hurley J, Doliny P, Reis I, Silva O, Gomez-Fernandez C, Velez P, et al. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2–positive locally advanced breast cancer. J Clin Oncol 2006;24:1883–8.

[22] Coudert BP, Largillier R, Arnould L, Chollet P, Campone M, Coeffic D, et al. Multicenter phase II trial of preoperative therapy with trastuzumab, docetaxel, and carboplatin for human epidermal growth factor receptor-2-overexpressing stage II or III breast cancer: Results of the GETN(A)-1 trial. J Clin Oncol 2007;25:2678–84.

[23] Buzdar AU, Valero V, Ibrahim NK, Francis D, Broglio KR, Theriault RL, et al. Pre-operative therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res 2007;13:228–33.

[24] Breast cancer. In: Greene FL, Page DL, Fleming ID et al, editors. Breast cancer, 6th ed. American Joint Committee on Cancer Staging Manual, Springer-Verlag New York, Inc., (2002).

[25] 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 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007:532.