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Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with *HER2*-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial

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Summary

Background—Neoadjuvant chemotherapy with trastuzumab for patients with *HER2*-positive breast cancer can produce a pathological complete response in the breast in 30–65% of patients. We investigated the effect of the timing of trastuzumab administration with anthracycline and taxane neoadjuvant chemotherapy.

Methods—This randomised trial was done at 36 centres in the USA and Puerto Rico. Women with operable *HER2*-positive invasive breast cancer were randomly assigned (1:1) with a biased coin minimisation algorithm, stratified for age, tumour size, and hormone receptor status. Neither patients nor investigators (except for a cardiac safety review panel) were masked to treatment

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Conflicts of interest

FM-B has been a speaker for Roche. The other authors declare that they have no conflicts of interest.

Contributors

AUB and KKH designed the study. AUB was the principal investigator and KKH was the coprincipal investigator. AUB, MSE, and VJS served on the cardiac review panel and reviewed all the safety data. AUB and KKH searched the published work. AUB, MSE, KKH, LMM, MR, and VJS collected, analysed, and interpreted data. VJS and LMM did the statistical analyses. MJE designed the study, enrolled patients, interpreted data, and reviewed the report. JCB collected data and revised the report. GU enrolled patients. FM-B collected data and reviewed the report. All authors wrote the report and approved the final version.

For the Cancer Trials Support Unit's Patient Enrollment Network Portal System see <https://www.ctsu.org>

assignment. Patients randomly assigned to sequential treatment received fluorouracil 500 mg/m², epirubicin 75 mg/m², and cyclophosphamide 500 mg/m² (FEC-75) on day 1 of a 21-day cycle for four cycles followed by paclitaxel 80 mg/m² and trastuzumab 2 mg/kg (after a 4 mg/kg loading dose) once per week for 12 weeks, while those randomly assigned to the concurrent treatment group received paclitaxel and trastuzumab once per week for 12 weeks followed by four cycles of FEC-75 (on day 1 of each 21-day cycle) and once-weekly trastuzumab, in the same doses as the sequential group. Surgery, including evaluation of the axilla, was done within 6 weeks of completion of neoadjuvant treatment. The primary outcome was the percentage of patients who had a pathological complete response in the intention-to-treat population. The study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00513292), number NCT00513292.

Findings—From Sept 15, 2007, to Dec 15, 2011, 282 women were enrolled (140 in the sequential group, 142 in the concurrent group). Two patients in the sequential group withdrew consent before starting treatment. 78 of 138 (56.5%, 95% CI 47.8–64.9) patients who received sequential treatment had a pathological complete response in the breast versus 77 of 142 (54.2%, 95% CI 45.7–62.6) who received concurrent treatment (difference 2.3%, 95% CI –9.3 to 13.9). No treatment-related deaths occurred. The most common severe toxic effects were neutropenia (35 [25.3%] of 138 patients in the sequential group vs 45 [31.7%] of 142 patients in the concurrent group) and fatigue (six [4.3%] vs 12 [8.5%]). Left ventricular ejection fraction dropped below the institutional lower limit of normal at week 12 in one (0.8%) of 130 patients who received sequential treatment and four (2.9%) of 137 patients who received concurrent treatment; by week 24, it had dropped below this limit in nine (7.1%) of 126 patients and in six (4.6%) of 130 patients, respectively.

Interpretation—Concurrent administration of trastuzumab with anthracyclines offers no additional benefit and is not warranted.

Introduction

Neoadjuvant chemotherapy can downstage the primary tumour and regional lymph nodes, making the tumour operable and enabling breast-conserving surgery in some patients.^{1,2} Neoadjuvant chemotherapy also enables quick assessment of the effectiveness of systemic treatment through evaluation of the pathological response in the primary tumour and lymph nodes.³ Pathological complete response in the breast and nodes after neoadjuvant chemotherapy is associated with favorable outcomes.² However, this association is limited to patients with intrinsic breast cancer subtypes: luminal B/*HER2*-negative, *HER2*-positive (non-luminal), and triple-negative disease.^{4,5}

Overexpression of *HER2* occurs in 25–30% of breast cancers and is associated with poor prognosis.^{6,7} Addition of trastuzumab to adjuvant systemic treatment for *HER2*-positive disease significantly reduces the risk of recurrence and death.^{8–10} However, concern exists about the cardiac safety profile of trastuzumab delivered concurrently with anthracyclines.¹¹

The effect of addition of trastuzumab to neoadjuvant systemic treatment is being investigated. A randomised phase 3 trial has assessed the effect of addition of trastuzumab to paclitaxel followed by fluorouracil 500 mg/m², epirubicin 75 mg/m², and cyclophosphamide 500 mg/m² (FEC-75) on day 1 of a 21-day cycle for four cycles each (four cycles of

paclitaxel and trastuzumab and four cycles of FEC-75 and trastuzumab) as neoadjuvant treatment for *HER2*-positive breast cancer.^{12,13} Addition of trastuzumab significantly increased the proportion of patients who had a pathological complete response (65% vs 26%) and improved disease-free survival ($p=0.041$). In another group of patients treated with the same regimen of concurrent trastuzumab and chemotherapy, 54.5% (95% CI 32.2–75.6) of patients had a pathological complete response.¹³ There were no safety concerns in either cohort.

On the basis of these findings, we designed the Z1041 trial to assess concurrent (paclitaxel and trastuzumab followed by concurrent trastuzumab and FEC-75) compared with sequential (FEC-75 followed by paclitaxel and trastuzumab) use of trastuzumab and FEC-75.

Methods

Study design and participants

Z1041 was a randomised controlled trial, done in 36 centres in the USA and Puerto Rico. We included women aged 18 years or older who had a diagnosis of invasive breast cancer made by a core needle biopsy. Eligibility criteria were Eastern Cooperative Oncology Group performance status of 0 or 1; breast lesion of 2.0 cm or more or at least one positive lymph node biopsy sample; *HER2*-positive disease (3+ by immunohistochemistry or amplification by fluorescence in-situ hybridisation); left ventricular ejection fraction (by multigated acquisition scan or, after protocol addendum number 4, by echocardiogram) 55% or more within 90 days of registration; and adequate blood chemistry results (absolute neutrophil count 1200 cell per μL , platelet count 100 000 platelets per μL , total bilirubin below institutional upper limit of normal, serum creatinine no greater than upper limit of normal, aspartate amino-transferase $1.5 \times$ upper limit of normal, and alkaline phosphatase $2.5 \times$ upper limit of normal).

Exclusion criteria were ipsilateral ductal carcinoma in situ treated with radiation; surgical axillary staging; metastatic disease; any current breast cancer treatment except hormonal treatment, which could be taken for up to 28 days after diagnosis but before study registration and had to be stopped before study registration; previous treatment with anthracyclines or taxanes; any investigational drug within 30 days of registration; history of myocardial infarction, congestive heart failure, cardio myopathy, or cardiac disease requiring drug treatment; severe conduction abnormality, valvular disease, cardio megaly, ventricular hypertrophy on electro cardio graphy, or poorly controlled hypertension; history of non-breast malignancy within 5 years of diagnosis of breast cancer; and sensory or motor neuropathy grade 2 or greater. Pregnant and breast-feeding women were ineligible. Women of child-bearing potential had a serum pregnancy test within 14 days of registration and agreed to use non-hormonal contraception during treatment.

Institutional review boards of the participating institutions approved the study. Participants gave written informed consent.

Randomisation and masking

Patients were registered and randomised with the Cancer Trials Support Unit's Patient Enrollment Network Portal System. Patients were randomly assigned to treatment (1:1) with a biased coin minimisation algorithm so that marginal distributions of stratification factors would be similar in each treatment group. Randomisation was stratified for extent of disease (breast lesion <2 cm and nodal metastases <2 cm vs breast lesion <2 cm and nodal metastases ≥ 2 cm vs breast lesion 2–4 cm vs breast lesion >4 cm), age (<50 years vs ≥ 50 years), hormone receptor status (oestrogen-receptor negative and progesterone-receptor negative vs oestrogen-receptor positive or progesterone-receptor positive or both). Neither patients nor investigators, except for a cardiac review panel, were masked to treatment assignment.

Procedures

Within 4 weeks of study entry, patients had baseline measurements of breast and nodal lesions. A bone scan was done if alkaline phosphatase was above the upper limit of normal. A liver scan was recommended if alkaline phosphatase or alanine aminotransferase concentrations were above the upper limit of normal. Chest CT, multigated acquisition scan, or echocardiography and electrocardiography were done within 3 months before study entry. Mammography of the ipsilateral breast within 6 months and of the contralateral breast within 12 months of study entry were also required.

Patients in the sequential treatment group were treated with fluorouracil 500 mg/m², epirubicin 75 mg/m², and cyclophosphamide 500 mg/m² (FEC-75) on day 1 of a 21-day cycle for four cycles followed by paclitaxel 80 mg/m² plus trastuzumab 4 mg/kg first dose and 2 mg/kg for subsequent doses on days 1, 8, and 15 of a 21-day cycle for four cycles.

Patients in concurrent treatment group were treated with paclitaxel 80 mg/m² and trastuzumab 4 mg/kg first dose and 2 mg/kg for subsequent doses on days 1, 8, and 15 of a 21-day cycle for four cycles followed by FEC-75 on day 1 of a 21-day cycle with trastuzumab 2 mg/kg on days 1, 8, and 15 of the 21-day cycle for four cycles.

Use of granulocyte colony-stimulating factor support was left to the discretion of the treating physician. If needed, filgrastim or pegfilgrastim was permitted during treatment with FEC, but pegfilgrastim was prohibited during paclitaxel treatment and filgrastim could be given on days 2–6 of a cycle. Erythropoietin was recommended if haemoglobin concentration fell below 100 g/L.

Before each cycle of treatment, patients had physical examination and assessments for blood chemistry, toxic effects, and tumour size. Left ventricular ejection fraction was measured by multigated acquisition scan or echocardiography at completion of the first 12-week regimen and second 12-week regimen. Each treating physician reported any cardiac events during and after completion of neoadjuvant treatment. A mammogram of the ipsilateral breast was taken at completion of neoadjuvant chemotherapy.

Two dose reductions were allowed. Treatment could not resume if toxic effects did not resolve to grade 1 within 3 weeks. Patients could have their dose reduced to level 1

(fluorouracil 400 mg/m², epirubicin 60 mg/m², and cyclophosphamide 400 mg/m²; paclitaxel 60 mg/m²) or level 2 (fluorouracil 400 mg/m², epirubicin 40 mg/m², and cyclophosphamide 400 mg/m²; paclitaxel 45 mg/m²).

Doses of both FEC and paclitaxel were reduced by one level for grade 2 vomiting, or increase in bilirubin, alanine aminotransferase, or alkaline phosphatase concentrations; grade 3 diarrhoea, stomatitis, or episodes of infection; or any significant grade 3 toxic effect. Doses were reduced by two levels for severe toxic effects. Paclitaxel dose was reduced by one level for grade 2 neurosensory toxic effects or musculoskeletal pain, two levels for grade 3, and discontinued for grade 4. Trastuzumab was discontinued for grade 3 acute infusion reaction, allergic reaction, cardiac ischaemia or infarction, arrhythmia, conduction abnormality, supraventricular or nodal arrhythmia, or ventricular arrhythmia. If left ventricular ejection fraction fell by 16% or more, or by 10–15% to below the lower limit of normal, trastuzumab was withheld for 4 weeks and then a multigated acquisition scan or echocardiography was done. If the resulting left ventricular ejection fraction met the criteria for withholding trastuzumab, trastuzumab was permanently discontinued.

The cardiac review panel (AUB, MSE, and VJS) reviewed multigated acquisition scan and echo cardiography results of all patients each month. A decrease of left ventricular ejection fraction from baseline of 15 percentage points or more, or more than 10 percentage points to a value below institutional lower limit of normal was classed as a substantial asymptomatic decrease. Asymptomatic decrease was deemed reversible if left ventricular ejection fraction recovered to a value 5 percentage points or less from baseline, partially reversible if it rose by more than 10 percentage points above nadir, but remained below baseline, indeterminate if a follow-up measurement was not available or time to follow-up was insufficient to permit assessment, or persistent if left ventricular ejection fraction continued to decrease or did not rise at least 10 percentage points above nadir. The data and safety monitoring board reviewed the trial every 6 months until data was released to the study team.

After surgery, patients entered a follow-up phase, in which disease status was assessed each year for a maximum of 5 years (data not shown). Adjuvant treatment was given at the discretion of the patient's physician. Patients were recommended to continue trastuzumab for a total duration of 1 year from the start of neoadjuvant treatment, but the schedule of administration of trastuzumab was modified to once every 3 weeks after surgery.

The primary endpoint was the proportion of patients who had a pathological complete response in the breast; a pathological complete response in the breast is no histological evidence of invasive tumour in the breast. Secondary endpoints were: pathological complete response in the breast and axillary nodes (percentage of women who started treatment and had no histological evidence of invasive tumour in the breast and axillary nodes at surgery), cardiac outcomes, adverse events, overall survival, and progression-free survival. Data for overall and progression-free survival are not yet mature, and will be reported later.

Statistical analysis

We calculated that 256 women (128 assigned to each regimen) needed to be enrolled for a 90% chance to detect a difference of more than 20% for the primary endpoint assuming that

the proportion of patients who would achieve a pathological complete response in the breast in the sequential group was no more than 25% and with a two-sided α of 0.05. We included all patients who began study treatment in the efficacy analyses. For each endpoint, we calculated a two sample 95% binomial CI for the difference in proportions between groups. We also compared odds ratios (ORs) between groups with a logistic regression model, stratified for age (<50 years vs 50 years), hormone receptor status (oestrogen-receptor positive or progesterone-receptor positive or both vs oestrogen-receptor negative or progesterone-receptor negative), and clinical T-stage (1 or 2 vs 3 or 4).¹⁴

Data were locked for analysis on May 12, 2013. Statistical analyses were done with SAS (version 9.3) at the Alliance Statistics and Data Center. Data quality was ensured by Alliance Statistics and Data Center and the study chairperson following Alliance policies.

This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT00513292.

Role of the funding source

The sponsor had no role in data collection, data analysis, data interpretation, or writing this report. The study was designed by the ACOSOG Breast Committee with input from the Cancer Therapy Evaluation Program of the US National Cancer Institute. VJS, LMM, and AUB had full access to all the raw data. AUB, VJS, and KKH had the final responsibility to submit for publication.

Results

From Sep 15, 2007, to Dec 15, 2011, we enrolled 282 women with *HER2*-positive breast cancer (figure). Six women were ineligible because pre-registration testing was not completed within the specified time frame (two patients), left ventricular ejection fraction was less than 55% (one patient), total bilirubin concentration was above the upper limit of normal (one patient), serum creatinine concentration was above the upper limit of normal (one patient), and left ventricular ejection fraction ascertained by echocardiogram before trial addendum number four (one patient). Two patients assigned to the sequential group withdrew consent before treatment. Table 1 shows baseline characteristics.

124 (89.9%) of 138 patients in the sequential treatment group and 121 (85.2%) of 142 in the concurrent treatment group received at least 90% of the planned dose of FEC-75. 103 (74.6%) in the sequential group and 123 (86.6%) in the concurrent group received at least 90% of the planned paclitaxel dose. 126 (91.3%) patients in the sequential group received at least 10 weeks of the planned 12 weeks of trastuzumab and 127 (89.4%) in concurrent group received at least 20 weeks of the planned 24 weeks of neoadjuvant trastuzumab. 55 (39.9%) patients in the sequential group versus 46 (32.4%) in the concurrent group had dose reductions; 18 (nine from each group) of these 101 patients subsequently discontinued neoadjuvant treatment because of intolerance (table 2).

Of 130 patients in the sequential group who underwent breast surgery, 49 (37.7%) had partial mastectomy, 18 (13.8%) had total mastectomy, and 63 (48.5%) had modified radical mastectomy (table 3). 78 (60.0%) patients had no residual disease in the breast. Of the 52

remaining patients, median residual tumor size was 1.2 cm (IQR 0.4–2.6) with negative margins for 45 of these patients. All but one patient who presented with clinical N0 disease (n=129) had axillary surgery. Of these patients, 39 (30.0%) had sentinel lymph-node dissection only and 90 (69.2%) had axillary dissection with or without sentinel lymph-node dissection. Only one of 46 patients (2.1%) with clinical N0 disease had a positive lymph node and 62 of 83 patients (74.7%) with clinical N1–3 disease had no positive lymph nodes at surgery.

Of 138 patients in the concurrent group who had breast surgery, 54 (39.1%) had partial mastectomy, 14 (10.1%) had total mastectomy, and 70 (50.7%) had modified radical mastectomy (table 3). 77 (55.8%) patients had no residual disease in the breast. Of the 61 remaining patients, median residual tumour size was 1.5 cm (IQR 0.5–3.5) with negative margins in 51 patients. 139 of 140 patients who presented with clinical N0 disease had axillary surgery. Of these patients, 39 (28.3%) had sentinel lymph node dissection alone and 98 (71.0%) patients had axillary dissection with or without sentinel lymph-node dissection. Six of 51 patients (11.8%) with clinical N0 disease had a positive lymph node and 55 of 86 patients (64.0%) with clinical N1–3 disease had no residual nodal involvement at the time of surgery).

78 (56.5%, 95% CI 47.8–64.9) of 138 women in the sequential treatment group had a pathological complete response) as did 77 (54.2%, 45.7–62.6) of 142 in the concurrent group. The estimated difference between groups was 2.3% (95% CI –9.3 to 13.9). The adjusted OR for pathological complete response in the breast in the concurrent versus the sequential group was 0.90 (95% CI 0.55–1.49).

38 (70.4%, 95% CI 56.4 to 82.0) of 54 women with oestrogen-receptor negative and progesterone-receptor negative breast cancer in the sequential group achieved a pathological complete response, as did 45 (77.6%, 95% CI 64.7 to 87.5) of the 58 such women in the concurrent group, with an estimated difference of –7.2% (95% CI –23.5 to 9.0). 40 (47.6%, 95% CI 36.6 to 58.8) of 84 women with oestrogen-receptor positive or progesterone-receptor positive breast cancer in the sequential group achieved a pathological complete response versus 32 (38.1%, 95% CI 27.7 to 49.3) of 84 such women in the concurrent group, with a difference of 9.5% (95% CI –5.3 to 24.4).

Of the 89 patients in the sequential group with clinical N1–3 disease, six (6.7%) did not undergo surgery; residual disease was found in neither the breast nor axilla of 43 (48.3%) patients, in only the breast of 19 (21.3%) patients, in only the axilla of five (5.6%) patients, and in both the breast and axilla of 16 (18.0%) patients. Thus, 48.3% (95% CI 37.6–59.2) of patients in the sequential group had a pathological complete response in the breast and axillary nodes.

In the concurrent group, 90 patients had clinical N1–3. Four patients (4.4%) did not undergo surgery. Residual disease was found in neither the breast nor axilla of 42 (46.7%) patients, in only the breast of 13 (14.4%) patients, in only the axilla of six (6.7%) patients, and in both the breast and axilla of 25 (27.8%) patients. Thus, 46.7% (95% CI 36.4–56.9) of

patients in the concurrent group had a pathological complete response in the breast and axillary nodes. The difference between groups was 1.6% (95% CI -13.0 to 16.3).

Table 4 shows left ventricular ejection fraction at baseline and changes during neoadjuvant treatment. At week 12, ventricular ejection fraction had fallen to below the institutional lower limit of normal for one (0.8%) patient in the sequential group and four (2.9%) in the concurrent group. At week 24, it was nine (7.1%) patients in the sequential group and six (4.6%) in concurrent group. The cardiac review panel reported asymptomatic decreases of left ventricular ejection fraction for 11 patients in the sequential group (five reversible, two partly reversible, three indeterminate, and one persistent) and for 15 patients in concurrent group (seven reversible, two partly reversible, and six indeterminate).

No treatment-related deaths occurred. 17 (12.3%) patients in the sequential group and 24 (16.9%) in the concurrent group were admitted to hospital for treatment-related toxic effects. 55 (39.9%) of 138 patients in the sequential group and 76 (53.5%) of 142 in the concurrent group had at least one severe adverse event (grades 3–4) reported to be possibly, probably, or definitely related to treatment. The most common severe toxic effects were neutropenia (35 [25.3%] vs 45 [31.7%]) and fatigue (six [4.3%] vs 12 [8.5%]; table 5).

Discussion

We found no improvement in breast pathological complete response in patients treated with concurrent paclitaxel and trastuzumab followed by concurrent FEC and trastuzumab compared with FEC alone followed by concurrent paclitaxel and trastuzumab. Additionally, substantial asymptomatic decreases of left ventricular ejection fraction during neoadjuvant chemotherapy occurred in similar proportions of patients in each group. However, because of the small sample size, differences between treatments in terms of cardiac tolerability during neoadjuvant treatment might not have been evident. Of note, our study does not provide information for the long-term effect on cardiac function of 12 weeks of trastuzumab with chemotherapy versus 24 weeks of trastuzumab with chemotherapy before surgery followed by 28–42 weeks of trastuzumab after surgery.

In the trial reported by Buzdar and colleagues,^{12,13} trastuzumab was delivered concurrently during both the paclitaxel and anthracycline phases of treatment, and trastuzumab plus chemotherapy was compared with chemotherapy alone. The findings from our trial indicate that trastuzumab does not need to be delivered concurrently with FEC-75 to achieve a high likelihood of pathological complete responses.

More patients had a pathological complete response in our trial than in several other studies. In GeparQuattro,¹⁵ patients were randomly assigned to one of three 12-week anthracycline and taxane regimens with concurrent trastuzumab given to those who had *HER2*-positive disease; 31.3–34.6% of patients had a pathological complete response. In the NOAH trial,¹⁶ patients received a 33-week regimen of doxorubicin plus paclitaxel followed by paclitaxel alone then trastuzumab with fluorouracil, methotrexate, and cyclophosphamide, resulting in a pathological complete response in 43% of patients. In the HannaH study,¹⁷ patients were randomly assigned to a 24-week regimen of trastuzumab administered either intravenously

or subcutaneously every 3 weeks concurrently with docetaxel followed by FEC; complete pathological responses were noted in 40.7–45.4% of patients. In a phase 2 trial¹⁸ of an 18-week regimen of docetaxel, cisplatin, and trastuzumab, complete pathological responses were seen in 44.8% of patients.

Several trials^{19–22} of neoadjuvant chemotherapy for *HER2*-positive breast cancer have assessed the addition of anti-*HER2* drugs, such as lapatinib or pertuzumab, concurrently with trastuzumab and taxane combinations. The addition of either lapatinib or pertuzumab increased the proportion of patients with a pathological complete response to 45–62%, albeit with increased toxic effects. The US Food and Drug Administration has approved pertuzumab and trastuzumab plus docetaxel as neoadjuvant treatment on the basis of significantly improved pathological complete responses (45.8%) reported in the phase 2 NeoSphere trial.¹⁹

The TRYPHAENA trial assessed pertuzumab plus trastuzumab in combination with anthracycline and taxane treatment and in combination with non-anthracycline-based treatment. Similar proportions of patients had pathological complete responses (54.7–63.6%, depending on the regimen) as in our study.²³ Thus, the challenge remains to define the best combinations and sequencing of anti-*HER2* drugs with taxanes in terms of efficacy and long-term effect on cardiac function. Understanding the basic biology that underlies sensitivity and resistance will help investigators develop rational combinations and sequences of drugs to further improve the likelihood of a pathological complete response.

The lack of information about how often granulocyte colony-stimulating factor and erythropoietin were used in each group limits the interpretation of the adverse events results. Furthermore, we do not have data from long-term follow-up. The effect of these regimens on disease-free and overall survival and long-term cardiac safety remains to be defined.

In our study, epirubicin was given at an attenuated dose of 75 mg/m² for four cycles. Our results confirms earlier findings that concurrent administration of trastuzumab and an anthracycline is not associated with an increased risk of cardiac dysfunction. However, in this trial it did not enhance the frequency of pathological complete response. Pathological complete response was similar for the two regimens, therefore, use of concurrent administration of anthracyclines with trastuzumab seems to provide no benefit in the neoadjuvant setting. Patients in the concurrent group received twice as much trastuzumab as those in the sequential group, yet the proportions of patients with a pathological complete response did not differ significantly. These findings are in accord with the TRYPHAENA trial,²³ in which 9 weeks versus 18 weeks of dual anti-*HER2* treatment did not significantly affect pathological complete response.

We have shown that anthracycline and taxane neoadjuvant chemotherapy with trastuzumab results in a complete pathological response in many patients with *HER2*-positive breast cancer. Pathological complete responses with concurrent versus sequential administration of trastuzumab in combination with FEC-75 were similar. Thus, concurrent administration of trastuzumab with anthracyclines offers no additional benefit and is not warranted (panel).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel: Research in context**Systematic review**

We searched PubMed with the terms “neoadjuvant therapy”, “HER-2/neu positive breast cancer”, and “pathological complete response” for studies published in English between Jan 1, 2005 and Aug 31, 2013. *HER2* is overexpressed in about 25–30% of breast cancers and is associated with a poor prognosis. A phase 3 randomised study¹² of neoadjuvant treatment for patients with *HER2*-positive disease used concurrent administration of trastuzumab with anthracyclines and taxanes and resulted in a substantial increase in pathological complete response compared with the same chemotherapy alone.¹² For treatment of metastatic disease, concurrent administration of anthracyclines and trastuzumab is associated with increased risk of cardiac dysfunction.¹¹

Interpretation

We found that the proportion of patients who achieved a pathological complete response was similar with concurrent versus sequential trastuzumab and fluorouracil, epirubicin, and cyclophosphamide. Thus, concurrent administration of trastuzumab with anthracyclines offers no additional benefit and is not warranted.

Figure. Trial profile

*The number of patients who were assessed for eligibility is unknown. †All patients who began neoadjuvant treatment were analysed. ‡Adjuvant treatment at discretion of the treating physician; protocol recommends trastuzumab every 3 weeks after surgery until the patient has completed 52 weeks of trastuzumab treatment (including trastuzumab given during neoadjuvant treatment) and a minimum of 5 years of hormonal treatment for participants with hormone receptor-positive tumours. Sequential treatment=fluorouracil, epirubicin, and cyclophosphamide followed by paclitaxel and trastuzumab. Concurrent treatment=paclitaxel and trastuzumab followed by fluorouracil, epirubicin, and cyclophosphamide, plus trastuzumab.

Table 1
Ba seline characteristics

	Sequential treatment group (n=138)	Concurrent treatment group(n=142)
Age (years)		
25–39	21 (15.2%)	21 (14.8%)
40–49	44 (31.9%)	47 (33.1%)
50–59	49 (35.5%)	55 (38.7%)
60–69	20 (14.5%)	15 (10.6%)
>70	4 (2.9%)	4 (2.8%)
Race (self-reported)		
White	118 (85.5%)	114 (80.3%)
Black or African American	13 (9.4%)	16 (11.3%)
Asian	3 (2.2%)	5 (3.5%)
American Indian or Alaska Native	2 (1.4%)	2 (1.4%)
Not reported	2 (1.4%)	5 (3.5%)
Ethnicity (self-reported)		
Hispanic or Latino	26 (18.8%)	38 (26.8%)
Not Hispanic or Latino	110 (79.7%)	101 (71.1%)
Not reported	2 (1.4%)	3 (2.1%)
Body-mass index		
<25.0 (underweight or normal)	43 (31.2%)	46 (32.4%)
25.0 (overweight or obese)	95 (68.8%)	96 (67.6%)
ECOG performance status		
0	129 (93.5%)	128 (90.1%)
1	9 (6.5%)	14 (9.9%)
Clinical T stage		
T1	8 (5.8%)	10 (7.0%)
T2	76 (55.1%)	78 (54.9%)
T3	41 (29.7%)	41 (28.9%)
T4	13 (9.4%)	13 (9.2%)
Clinical N stage		
N0	49 (35.5%)	52 (36.6%)
N1	71 (51.5%)	82 (57.7%)
N2	7 (5.1%)	7 (4.9%)
N3	11 (8.0%)	1 (0.7%)
Hormone receptor status		
ER positive, PR positive	49 (35.5%)	59 (41.5%)
ER positive, PR negative	31 (22.5%)	23 (16.2%)

	Sequential treatment group (n=138)	Concurrent treatment group(n=142)
ER negative, PR positive	4 (2.9%)	2 (1.4%)
ER negative, PR negative	54 (39.1%)	58 (40.8%)
Tumour grade		
1	2 (1.4%)	4 (2.8%)
2	58 (42.0%)	47 (33.1%)
3	77 (55.8%)	91 (64.1%)
Unknown	1 (0.7%)	0 (0%)
Histology		
Ductal	131 (94.9%)	138 (97.2%)
Lobular	3 (2.2%)	1 (0.7%)
Mammary	2 (1.4%)	2 (1.4%)
Tubular	0 (0%)	1 (0.7%)
Not specified	2 (1.4%)	0 (0%)
Baseline LVEF measurement method		
Multigated acquisition scan	100 (72.5%)	102 (71.8%)
Echocardiography	38 (27.5%)	40 (28.2%)
Baseline LVEF (%)		
50–54	1 (0.7%)	1 (0.7%)
55–59	24 (17.4%)	15 (10.6%)
60–64	42 (30.4%)	45 (31.7%)
65–69	48 (34.8%)	48 (33.8%)
70–85	23 (16.7%)	33 (23.2%)
History of hypertension	37 (26.8%)	35 (24.6%)
Taking drugs for		
Cardiovascular disease	11 (8.0%)	15 (10.6%)
Diabetes	11 (8.0%)	15 (10.6%)
Hyperlipidaemia	21 (15.2%)	17 (12.0%)

Data are n (%). ECOG=Eastern Cooperative Oncology Group. ER=oestrogen receptor. LVEF=left ventricular ejection fraction. N=nodal. PR=progesterone receptor. T=tumour. Sequential treatment=fluorouracil, epirubicin, and cyclophosphamide followed by paclitaxel and trastuzumab. Concurrent treatment=paclitaxel and trastuzumab followed by fluorouracil, epirubicin, and cyclophosphamide, plus trastuzumab.

Table 2
Reason for discontinuing neoadjuvant treatment

	Sequential treatment group (n=138)	Concurrent treatment group (n=142)
Proceeded directly to surgery		
Refused	2 (1.4%)	0 (0%)
Physician discretion	1 (0.7%)	0 (0%)
Insurance problems	0 (0%)	1 (0.7%)
Disease progression	1 (0.7%)	1 (0.7%)
Severe toxic effects	9 (6.5%)	9 (6.3%)
Grade 2 neuropathy	3	0
Grade 3 neuropathy	3	1
Grade 3 dehydration	1	0
Grade 3 allergic reaction	1	1
Grade 3 anorexia or hyperglycaemia	0	1
Grade 3 hyperglycaemia	0	1
Grade 2 left ventricular systolic dysfunction	1	1
Grade 3 atrial fibrillation and grade 2 left ventricular systolic dysfunction	0	1
Grade 4 cardiac ischaemia and grade 3 left ventricular systolic dysfunction	0	1
Persistent neutropenia	0	1
15-point drop in left ventricular ejection fraction	0	1
Did not undergo surgery		
Physician discretion	2 (1.4%)	0 (0%)
Refused to continue with neoadjuvant treatment	4 (2.9%)	2 (1.4%)
Allergic reaction	0 (0%)	1 (0.7%)
Disease progression	0 (0%)	1 (0.7%)
Second primary cancer	1 (0.7%)	0 (0%)
Death	1 (0.7%)*	0 (0%)

Sequential treatment=fluorouracil, epirubicin, and cyclophosphamide followed by paclitaxel and trastuzumab. Concurrent treatment=paclitaxel and trastuzumab followed by fluorouracil, epirubicin, and cyclophosphamide, plus trastuzumab.

* Autopsy indicated carisoprodol toxicity and death was deemed accidental.

Table 3
Types of surgery and pathology findings

	Sequential treatment group (n=130)	Concurrent treatment group (n=138)
Breast surgery		
Partial mastectomy	49 (37.7%)	54 (39.1%)
Total mastectomy	18 (13.8%)	14 (10.1%)
Modified radical mastectomy	63 (48.5%)	70 (50.7%)
Axillary lymph-node surgery		
None	1 (0.8%)	1 (0.7%)
Sentinel lymph-node dissection only	39 (30.0%)	39 (28.3%)
Axillary lymph-node dissection with or without sentinel lymph-node dissection	90 (69.2%)	98 (71.0%)
Residual tumour size (cm)		
Microinvasion–1.0	24 (18.5%)	22 (15.9%)
1.1–2.0	14 (10.8%)	14 (10.1%)
2.1–5.0	11 (8.5%)	17 (12.3%)
5.1	3 (2.3%)	8 (5.8%)
No residual tumour	78 (60.0%)	77 (55.8%)
Number of positive lymph nodes		
0	107 (82.3%)	100 (72.5%)
1–3	20 (15.4%)	25 (18.1%)
4–9	1 (0.8%)	9 (6.5%)
10	1 (0.8%)	3 (2.2%)
Not evaluated	1 (0.8%)	1 (0.7%)

Data are n (%). Sequential treatment=fluorouracil, epirubicin, and cyclophosphamide followed by paclitaxel and trastuzumab. Concurrent treatment=paclitaxel and trastuzumab followed by fluorouracil, epirubicin, and cyclophosphamide, plus trastuzumab.

Table 4
Left ventricular ejection fraction

	Sequential treatment group	Concurrent treatment group
At baseline	n=138	n=142
Median (IQR)	65% (61 to 67)	65% (62 to 69)
Week 12	n=130	n=137
Median change from baseline (IQR)	2% (−5 to 2)	3% (−7 to 0)
LVEF measurement (n, %)		
No decrease or decrease <10%, still <LLN	120 (92.3%)	113 (82.5%)
Decrease <10%, below LLN	1 (0.8%)	0 (0%)
Decrease 10–15%, still above LLN	8 (6.2%)	16 (11.7%)
Decrease 10–15%, below LLN	0 (0%)	0 (0%)
Decrease >15%, still above LLN	1 (0.8%)	4 (2.9%)
Decrease >15%, below LLN	0 (0%)	4 (2.9%)
Week 24	n=126	n=130
Median change from baseline (IQR)	−3% (−7 to 0)	−4% (−9 to 0)
LVEF measurement (n, %)		
No decrease or decrease <10%, still <LLN	105 (83.3%)	95 (73.1%)
Decrease <10%, below LLN	1 (0.8%)	4 (3.1%)
Decrease 10–15%, still above LLN	10 (7.9%)	20 (15.4%)
Decrease 10–15%, below LLN	3 (2.4%)	1 (0.8%)
Decrease >15%, still above LLN	2 (1.6%)	9 (6.9%)
Decrease >15%, below LLN	5 (4.0%)	1 (0.8%)

Data are median (IQR) or n (%) unless stated otherwise. LLN=lower limit of institutional normal. LVEF=left ventricular ejection fraction.

Sequential treatment=fluorouracil, epirubicin, and cyclophosphamide followed by paclitaxel and trastuzumab. Concurrent treatment=paclitaxel and trastuzumab followed by fluorouracil, epirubicin, and cyclophosphamide, plus trastuzumab.

Table 5
Cardiac and most common adverse events reported as possibly, probably, or definitely related to treatment

	Sequential treatment group (n=138)				Concurrent treatment group (n=142)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Haematological								
Anaemia	28 (20.3%)	16 (11.6%)	3 (2.2%)	1 (0.7%)	24 (16.9%)	19 (13.4%)	3 (2.1 %)	0 (0%)
Leucocytopenia	11 (8.0%)	15 (10.9%)	2 (1.4%)	2 (1.4%)	7 (4.9%)	13 (9.2%)	9 (6.3%)	5 (3.5 %)
Lymphopenia	2 (1.4%)	7 (5.1 %)	4 (2.9%)	0 (0%)	3 (2.1%)	6 (4.2%)	7 (4.9%)	0 (0%)
Neutropenia	14 (10.1%)	16 (11.6 %)	21 (15.2%)	14 (10.1%)	9 (6.3%)	20 (14.1%)	27 (19.0%)	18 (12.7%)
Non-haematological, non-cardiac								
Diarrhoea	34 (24.6%)	22 (15.9 %)	3 (2.2%)	0 (0%)	52 (36.6%)	21 (14.8%)	4 (2.8%)	0 (0%)
Fatigue	64 (46.4%)	51 (37.0%)	6 (4.3%)	0 (0%)	53 (37.3%)	56 (39.4%)	12 (8.5%)	0 (0%)
Hyperglycaemia	5 (3.6%)	1 (0.7 %)	2 (1.4%)	1 (0.7%)	6 (4.2%)	4 (2.8%)	2 (1.4%)	0 (0%)
Hypokalaemia	6 (4.3%)	1 (0.7%)	3 (2.2%)	0 (0%)	13 (9.2%)	1 (0.7%)	1 (0.7%)	0 (0%)
Nausea	58 (42.0%)	33 (23.9%)	3 (2.2%)	0 (0%)	60 (42.3%)	38 (26.8%)	3 (2.1%)	0 (0%)
Neurosensory difficulties	60 (43.5%)	17 (12.3%)	5 (3.6%)	0 (0%)	68 (47.9%)	21 (14.8%)	7 (4.9%)	0 (0%)
Cardiac								
Atrial fibrillation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)
Cardiac ischaemia or infarction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	1 (0.7%)
Hypertension	5 (3.6%)	3 (2.2%)	1 (0.7%)	0 (0%)	12 (8.5%)	2 (1.4%)	1 (0.7%)	0 (0%)
Left ventricular systolic dysfunction	1 (0.7%)	4 (2.9%)	0 (0%)	0 (0%)	6 (4.2%)	5 (3.5%)	1 (0.7%)	0 (0%)
Supraventricular tachycardia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)

Data are n (%). Sequential treatment=fluorouracil, epirubicin, and cyclophosphamide followed by paclitaxel and trastuzumab. Concurrent treatment=paclitaxel and trastuzumab followed by fluorouracil, epirubicin, and cyclophosphamide, plus trastuzumab.