# Adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with *HER2*-amplified early stage breast cancer: a single-group, open-label, phase 2 study

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## Summary

**Background** Previous results suggest that docetaxel plus cyclophosphamide improves disease-free survival (DFS) and overall survival compared with doxorubicin plus cyclophosphamide in early stage breast cancer. We assessed the addition of 1 year of trastuzumab to a non-anthracycline regimen, docetaxel plus cyclophosphamide, in patients with *HER2*-amplified early stage breast cancer and examined whether this regimen was equally effective in patients with *TOP2A*-amplified and *TOP2A*-non-amplified disease.

**Methods** This was an open-label, single-group, phase 2 study. Eligible patients were aged 18–75 years; had Eastern Cooperative Oncology Group performance status of 1 or less; *HER2*-amplified early stage breast cancer; operable, histologically confirmed, invasive carcinoma of the breast; adequate tumour specimen available for FISH analysis of *TOP2A* status; and adequate haematological, renal, hepatic, and cardiac function. Patients received four 21-day cycles of intravenous docetaxel 75 mg/m², plus intravenous cyclophosphamide 600 mg/m², plus intravenous trastuzumab 4 mg/kg (loading dose) on day 1 and 2 mg/kg on days 1, 8, and 15 during chemotherapy, followed by trastuzumab 6 mg/kg every three weeks for the remainder of 1 year. The primary endpoint was 2-year DFS in *TOP2A*-amplified and *TOP2A*-non-amplified patients; the primary analysis was done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00493649.

**Findings** 493 patients were enrolled between June 15, 2007, and Aug 5, 2009. After a median follow-up of 36·1 months (IQR 35·5–36·7), 2-year DFS was 97·8% (95% CI 94·2–99·2) and 2-year overall survival was 99·5% (95% CI 96·2–99·9) for the 190 patients with *TOP2A*-amplified disease; 2-year DFS was 97·9% (95% CI 94·9–99·1) and 2-year overall survival was 98·8% (95% CI 96·2–99·6) for the 248 patients with *TOP2A*-non-amplified disease; 55 patients were not assessable for *TOP2A* status. In the 486 patients who received at least one dose of study drug, the most common adverse events of any grade were fatigue (284 patients, 58·4%), neutropenia (250, 51·4%), and nausea (217, 44·7%). The most common grade 3–4 toxic effects were neutropenia (229, 47·1%), febrile neutropenia (30, 6·2%), fatigue (21, 4·3%), and diarrhoea (16, 3·3%). Cardiac dysfunction occurred in 29 (6·0%) patients (12 [2·5%] grade 1, 15 [3·1%] grade 2, and two [0·4%] grade 3). 23 patients had at least one study-related serious adverse event. 16 patients stopped trastuzumab because of cardiac dysfunction.

**Interpretation** A short, four-cycle regimen of docetaxel and cyclophosphamide combined with trastuzumab could be an option for adjuvant treatment of women with lower risk *HER2*-amplified early breast cancer, irrespective of *TOP2A* status.

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## Introduction

Taxanes were introduced into clinical practice for metastatic breast cancer and adjuvant treatment in the early 1990s.[1–3] Before the arrival of taxanes, four cycles of doxorubicin and cyclophosphamide was the standard adjuvant treatment for breast cancer. The regimen of doxorubicin and cyclophosphamide, given every 3 weeks, had equivalent efficacy to 6 months of cyclophosphamide, methotrexate, and fluorouracil.[4,5] So far, no regimen administered for four cycles has matched the effectiveness of doxorubicin and cyclophosphamide. However, these drugs can be cardiotoxic and are associated with myelodysplasia and leukaemia.

Docetaxel has been shown to improve overall survival, time to progression, and overall response rate compared with paclitaxel when given every 3 weeks to patients with metastatic breast cancer.[6] Valero[7] studied docetaxel and cyclophosphamide in 39 patients with advanced solid tumours, some of which were breast tumours, to establish the maximum tolerated doses, toxic effects, pharmacokinetics, and efficacy of these drugs in combination. The dose-limiting toxic effect was neutropenic fever, not cardiotoxicity.[7]

With these data available, US Oncology Research did an adjuvant chemotherapy study in 1016 patients with stage I to III, operable invasive breast cancer.[8] Four

cycles of docetaxel and cyclophosphamide were compared with standard doxorubicin and cyclophosphamide to assess disease-free survival (DFS). 5-year DFS with docetaxel and cyclophosphamide was 86%, compared with 80% with doxorubicin and cyclophosphamide (hazard ratio [HR] 0·67, 95% CI 0·50–0·94, p=0·015). At 7 years, DFS was 81% for docetaxel and cyclophosphamide versus 75% for doxorubicin and cyclophosphamide (p=0·03), and overall survival was 87% for docetaxel and cyclophosphamide versus 82% for doxorubicin and cyclophosphamide (p=0·03).[9] Docetaxel and cyclophosphamide seemed to be more effective than doxorubicin and cyclophosphamide in a subgroup analysis of patients with *HER2*-amplified breast cancer treated without trastuzumab.[9] Trastuzumab has been shown to be effective in combination with anthracycline-based adjuvant regimens, but anthracyclines and trastuzumab are cardiotoxic.

*TOP2A*, the gene positioned next to *HER2*,[10] whether amplified or deleted, might predict a patient's response to anthracyclines.[11,12] When this study was conceived, there were retrospective data for an association between *TOP2A* status and benefit from anthracyclines, but the most compelling data came from the Breast Cancer International Research Group (BCIRG) trial[13] in which anthracycline benefit seemed to be related to *TOP2A* overexpression only in *HER2*-amplified breast cancer.[12] However, some researchers have suggested that TOP2A protein expression might better relate to anthracycline benefit than gene amplification.[14] Additionally, at the time of planning the study, there were two conflicting datasets for *c-MYC* gene expression and outcome.[15,16] Therefore, in the present study, we assessed the addition of 1 year of trastuzumab to docetaxel plus cyclophosphamide in patients with *HER2*-amplified early stage breast cancer and included an analysis of *TOP2A* and *c-MYC* gene copy number, assessed in a central reference laboratory, to examine the effect of expression of these genes on outcome in patients given a non-anthracycline regimen.[9]

## Methods

### Study design and participants

We did this single-group, open-label, phase 2 study of adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with *HER2*-amplified early stage breast cancer in the US Oncology Research network of outpatient cancer clinics across the USA.

Eligible participants were women aged between 18 and 75 years with *HER2*-amplified (local institutional criteria either by immunohistochemistry or fluorescence in-situ hybridisation [FISH]), operable, histologically confirmed invasive breast cancer; known oestrogen receptor and progesterone receptor status; adequate tumour specimen available for FISH analysis of *HER2*, *TOP2A*, and *c-MYC* status; no previous chemotherapy unless received more than 5 years earlier; and European Cooperative Oncology Group performance status of 0–1. The primary breast tumour must have been completely removed, either by lumpectomy or mastectomy with sentinel lymph node or axillary dissection, done up to 84 days earlier with adequate wound healing. Cardiac function had to be within normal limits (left ventricular ejection fraction [LVEF] ≥50%), as established by multigated acquisition scan or echocardiography. For the node-negative population, no lower limit of tumour size was required. Patients must have had acceptable laboratory findings, and must have had a negative pregnancy test done within 7 calendar days before registration if clinically warranted.

We excluded patients if they had stage IIIA (T0, N2, M0; T1 including T1mi, N2, M0; T2, N2, M0; T3m, N1, M0; T3, N2, M0), stage IIIB (T4, N0, M0; T4, N1, M0; T4, N2, M0),[17] or locally advanced breast cancer; stage IV breast cancer; evidence of disease after complete surgical resection of the primary tumour and metastatic workup; previous chemotherapy within the past 5 years; a history of severe hypersensitivity reaction to drugs formulated with polysorbate 80; were receiving concurrent immunotherapy, hormonal therapy, or radiation therapy; had peripheral neuropathy of higher than grade 1; were receiving concurrent investigational therapy, or had received this therapy within the preceding 30 days.

The protocol was amended on Sept 11, 2007, to exclude patients with four or more positive nodes. Before this amendment, three patients with four or more positive nodes were enrolled and their data are included in the final analysis. After the amendment date, three patients with four or more positive nodes were screened. Two of these were ineligible; a deviation request was submitted for the third patient, this patient was enrolled and included in the final analysis.

All participants signed informed consent and authorisation forms before enrolment. The central institutional review board of the US Oncology Network (McKesson Specialty Health) approved this study, which complies with good clinical practice guidelines.

### Procedures

Within 3 weeks of registration, patients had to be shown to meet all the inclusion criteria and none of the exclusion criteria and complete all laboratory assessments and medical and physical examinations. Radiological assessment of tumour status was done, which included a chest radiograph or other imaging of the chest (chest CT, CT-PET, MRI, PET). A complete blood count, complete metabolic profile, and electrocardiogram were obtained when clinically indicated.

Patients received four 21-day cycles of intravenous docetaxel 75 mg/m² (over 1 h), plus intravenous cyclophosphamide 600 mg/m² (over 15–30 min), plus intravenous trastuzumab 4 mg/kg (loading dose over 90 min) on day 1, cycle one only, and intravenous trastuzumab 2 mg/kg (over 30–60 min) on days 1, 8,

and 15 thereafter. Patients continued to receive trastuzumab 6 mg/kg every 3 weeks to complete 1 year of anti-HER2 therapy, as per the present standard of care. The first dose of trastuzumab 6 mg/kg was begun 7 days after day 15 of cycle four. Use of white blood cell growth factors (eg, pegfilgrastim or filgrastim) was permitted. Prophylactic oral antibiotics were not recommended. All drugs were administered according to package insert recommendations.

Dose reductions were based on the initial drug dose and the degree of toxic effect; for –1 level dose reduction, docetaxel was lowered to 60 mg/m² and cyclophosphamide was lowered to 500 mg/m². Only one dose reduction was allowed for docetaxel and cyclophosphamide. If dose reductions of these two drugs were necessary, these reductions were permanent. No dose reductions were allowed for trastuzumab. If unacceptable toxic effects occurred with trastuzumab, this drug was discontinued. Appropriate hormonal therapy was given for at least 5 years to all women who were oestrogen-receptor positive or progesterone-receptor positive. The type of hormonal therapy was administered at the discretion of the treating physician.

All patients who had a segmental mastectomy and some patients who had a mastectomy were given radiotherapy in accordance with institutional or practice radiation therapy guidelines after completion of all chemotherapy.

Patients were followed up for 3 years. The study was completed when all patients had 3 years of follow-up.

All adverse events of grade 3 or 4, alopecia of grade 1 or 2, and cardiac toxic effects and neutropenia of all grades were recorded throughout the study and for up to 30 days after the date of the last study treatment. Toxic effects and adverse events were graded and reported using the Common Terminology Criteria for Adverse Events (version 3.0).[18]

Cardiac toxic effects, defined as a decrease in LVEF, were assessed by multigated acquisition or echocardiography at baseline, at the completion of docetaxel, cyclophosphamide, and trastuzumab treatment, and then at 3 month intervals until the completion of trastuzumab treatment, using the same technique at the same laboratories throughout the study period.

To do tumour biomarker assays, tissue samples were requested for each patient and sent to the central Caris Life Sciences laboratory (Phoenix, AZ, USA). These samples consisted of one paraffin block from a representative area of the tumour, and were made into unstained sections or tissue arrays. For those institutions that did not allow blocks to be sent, at least 10–15 unstained, 4 µm thick specimens mounted on charged (or silanated) slides for immunostaining were provided to Caris for analysis of gene copy number of *HER2*, *c-MYC*, and *TOP2A*. Genes were defined as amplified when the FISH ratio was 2 or greater, or deleted when the FISH ratio was 1 or lower.[12,14]

The primary outcome was DFS at 2 years in patients with *TOP2A*-amplified disease and in those with *TOP2A*-non-amplified disease. Secondary outcomes were 3-year DFS, overall survival, and safety. DFS was defined as the time from the date of registration to disease recurrence or death attributable to any cause if it happened before recurrence. If a recurrence or death did not occur, the patient was censored on the date of last contact. Overall survival was defined as the time from the date of registration to death or the last contact for censored patients.

### Statistical analysis

Using STPLAN (version 4.5), we calculated that a single-group clinical trial with one-sided α of 0·05 and power of 80% needed to enrol 130 patients with *TOP2A*-non-amplified disease to show an improvement from 83%[13] to 91% in DFS at 2 years. The same number of patients was needed for *TOP2A*-amplified disease. After 260 patients were enrolled, 233 additional patients were registered to test the assumption that the proportion of patients free of cardiac events would increase from 96·2% to 98·2%.[18]

DFS and overall survival were estimated using the Kaplan-Meier[19] method for all patients, for the *TOP2A*-non-amplified and *TOP2A*-amplified groups, and for the *c-MYC*-amplified and *c-MYC*-non-amplified groups.

| | Patients (N=493) |
|---|---|
| Age (years) | 55 (24–75) |
| ECOG performance status | |
| 0 | 431 (87·4%) |
| 1 | 62 (12·6%) |
| Stage at diagnosis | |
| I | 284 (57·6%) |
| II | 203 (41·2%) |
| III | 6 (1·2%) |
| Positive nodes | |
| None | 391 (79·3%) |
| 1–3 | 96 (19·5%) |
| ≥4 | 6 (1·2%) |
| Tumour size (cm) | |
| <0·5 | 17 (3·4%) |
| 0·5–1·0 | 90 (18·3%) |
| 1·1–2·0 | 224 (45·4%) |
| 2·1–5·0 | 162 (32·9%) |
| Oestrogen receptor status | |
| Negative | 173 (35·1%) |
| Positive | 320 (64·9%) |
| Progesterone receptor status | |
| Negative | 260 (52·7%) |
| Positive | 233 (47·3%) |

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group.

***Table 1:*** **Baseline characteristics**

Analyses of DFS and overall survival were by intention to treat.[20] The toxic effect profile of docetaxel, cyclophosphamide, and trastuzumab was assessed in the safety population, defined as all patients who received at least one dose of study drug. The association between DFS and potential prognostic factors were investigated by multivariate analysis using a Cox regression model with age, *TOP2A*, *c-MYC*, nodes, oestrogen receptor, and T status as covariates.

We used SAS (version 9.2) for the analyses, and R (version 2.13.0) to prepare survival analysis figures. This study is registered with ClinicalTrials.gov, number NCT00493649.

### Role of the funding source

The sponsor approved the study design, but did not participate in its development. The sponsor had no role in data collection, data analysis, or data interpretation. Sanofi reviewed the study report, but did not have a role in writing it. Only corresponding author (SEJ) had full access to all the data in the study. SEJ had final responsibility for the decision to submit for publication.

## Results

Between June 15, 2007, and August 5, 2009, 493 patients were registered in the study. Median age was 55 years (range 24–75) and most participants (414, 84·0%) were white. Table 1 shows baseline demographic characteristics. Of 493 registered patients, 486 received treatment; of these, 397 patients (81·7%) completed 1 year of trastuzumab, 461 (94·9%) patients completed all four cycles of cyclophosphamide, and 458 (94·2%) patients completed all four cycles of docetaxel.

Of the 493 patients enrolled, 438 tissue samples were available for FISH analysis of gene copy number at Caris Life Sciences central laboratory. Although all cases were classified as *HER2*-amplified at the local institutional level, *HER2* amplification was confirmed in 432 (87·6%) of 493 samples at the central laboratory. Subanalysis by central review showed no differences in T, N, and outcome between patients with *HER2*-amplified confirmed disease versus those in whom *HER2*-amplified disease was not confirmed. Results for *TOP2A* and *HER2* were generated for 438 samples; results for *c-MYC* were generated for 436 samples. *TOP2A* was classified as amplified in 190 (43·4%) samples, normal in 130 (29·7%), and deleted in 118 (26·9%). *c-MYC* was classified as amplified in 99 (22·7%), normal in 246 (56·4%), and deleted in 91 (20·9%).

Of the 493 patients, eight died (main cause of death was disease progression) and median follow-up for the 485 living patients was 36·1 months (IQR 35·5–36·7). By this point, there had been 15 recurrences of breast cancer, of which five were local, nine were distant, and one was local-distant. 2-year DFS was 97·8% (95% CI 94·2–99·2) and 2-year overall survival was 99·5% (95% CI 96·2–99·9) for the 190 patients with *TOP2A*-amplified disease; 2-year DFS was 97·9% (95% CI 94·9–99·1) and 2-year overall survival was 98·8% (95% CI 96·2–99·6) for the 248 patients with *TOP2A*-non-amplified disease (table 2). For all 493 patients, 2-year DFS was 97·8% (95% CI 96·0–98·8) and 2-year overall survival was 99·2% (95% CI 97·8–99·7; figure 1, table 2). DFS and overall survival by node status, tumour size, and gene status are shown in table 2. Because there was no lower limit of tumour size, 95 patients with negative nodes and tumour of 1 cm or smaller were included—they had a DFS and overall survival of 100% at 2 years and 3 years. Gene copy number had no effect on DFS or overall survival.

Multivariate analysis showed that node positivity (hazard ratio [HR] 2·66, 95% CI 0·91–7·82, p=0·08) and oestrogen-receptor-negativity (HR 0·41 for

| | 2-year DFS | 3-year DFS | 2-year overall survival | 3-year overall survival |
|---|---|---|---|---|
| All patients (n=493) | 97·8% (96·0–98·8) | 96·9% (94·8–98·1) | 99·2% (97·8–99·7) | 98·7% (97·1–99·4) |
| Node status | | | | |
| Node positive (n=102) | 96·9% (90·7–99·0) | 93·5% (86·2–97·1) | 100% | 97·7% (91·3–99·4) |
| Node negative (n=391) | 98·1% (96·0–99·1) | 97·8% (95·6–98·9) | 98·9% (97·2–99·6) | 98·9% (97·2–99·6) |
| ≤1·0 cm node negative (n=95) | 100% | 100% | 100% | 100% |
| Tumour size | | | | |
| ≤1·0 cm (n=107) | 100% | 100% | 100% | 100% |
| 1·1–2·0 cm (n=224) | 98·1% (95·0–99·3) | 96·5% (92·8–98·3) | 99·5% (96·8–99·9) | 99·5% (96·8–99·9) |
| >2·0 cm (n=162) | 96·0% (91·3–98·2) | 95·2% (90·2–97·7) | 98·1% (94·1–99·4) | 96·6% (92·0–98·6) |
| Gene copy number | | | | |
| *TOP2A* amplified (n=190) | 97·8% (94·2–99·2) | 97·2% (93·4–98·8) | 99·5% (96·2–99·9) | 98·9% (95·6–99·7) |
| *TOP2A* non-amplified (n=248) | 97·9% (94·9–99·1) | 96·4% (92·9–98·2) | 98·8% (96·2–99·6) | 98·3% (95·4–99·3) |
| *cMYC* amplified (n=99) | 96·8% (90·4–99·0) | 96·8% (90·4–99·0) | 99·0% (93·0–99·9) | 99·0% (93·0–99·9) |
| *cMYC* non-amplified (n=337) | 98·1% (95·8–99·1) | 97·1% (94·4–98·5 ) | 99·1% (97·2–99·7) | 98·8% (96·7·99·5) |

Data are % (95% CI). DFS=disease-free survival.

***Table 2:*** **Summary of 2-year and 3-year DFS and overall survival by pathological feature or gene copy number**

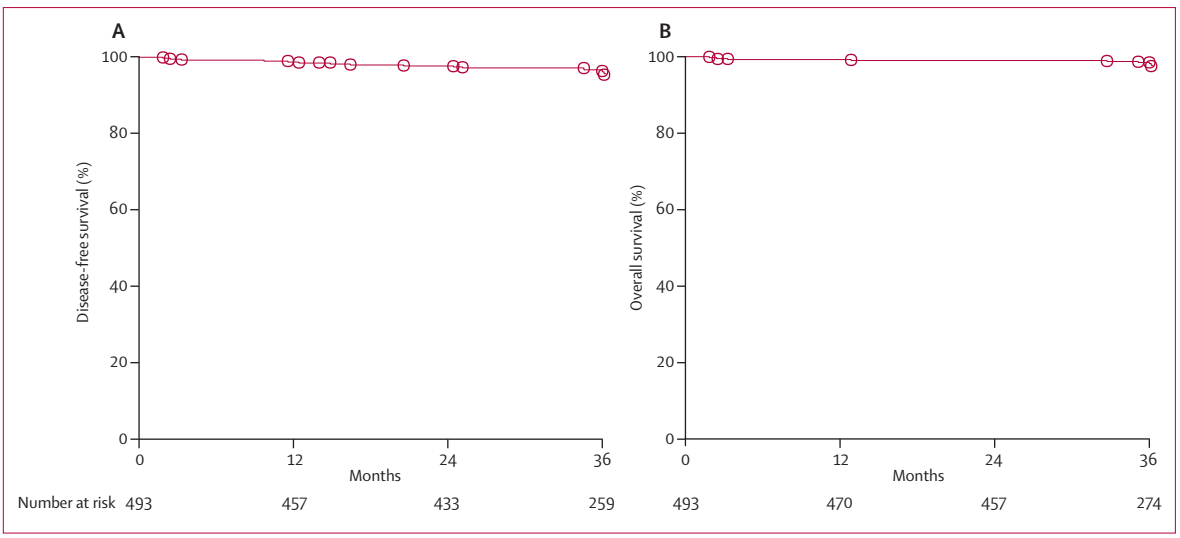


***Figure 1:*** **Disease-free survival and overall survival in the intention-to-treat population**
(A) Disease-free survival. (B) Overall survival.

oestrogen-receptor-positive vs oestrogen-receptor-negative, 95% CI 0·14–1·19, p=0·10) were potential prognostic factors of DFS, but none of these factors were statistically significant. There were too few events for a multivariate analysis of overall survival.

The most common adverse events of any grade occurring in the 486 patients who received at least one dose of study drug were fatigue, neutropenia, and nausea (table 3). Febrile neutropenia was reported in 34 (7·0%) patients. The most common grade 3–4 adverse events were neutropenia, anaemia, fatigue, and diarrhoea (table 3). On the basis of clinical judgment, pegfilgrastim was used in 151 (31·1%) of 486 patients in cycle one, 223 (45·9%) patients in cycle two, 203 (41·8%) patients in cycle three, and 190 (39·1%) patients in cycle four. 291 (59·9%) patients received pegfilgrastim for at least one cycle.

23 patients had at least one study-related serious adverse event. Dose reductions were needed in 38 (7·8%) of 486 patients. 40 (8·2%) patients discontinued study treatment because study-related adverse events, and two patients died from treatment-related causes, one from aspiration and one from pulmonary infiltration.

Figure 2 and table 4 show LVEF data for the safety population over time. Of these patients, 25 (5·1%) had decreased LVEF to less than 50%. 117 (24·1%) patients had a decrease of 10% in LVEF at some point in the study. Other cardiac events were rare, occurring in 29 (6·0%) patients (12 [2·5%] grade 1, 15 [3·1%] grade 2, and two [0·4%] grade 3). 16 patients stopped treatment because of cardiac dysfunction. Of these 16 patients, five had cardiac dysfunction that resolved, ten had persistent cardiac dysfunction, and one died due to cardiopulmonary arrest unrelated to study treatment. One patient was reported to have congestive heart failure.

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Haematological** | | | | |
| Neutropenia | 8 (1·6%) | 13 (2·7%) | 55 (11·3%) | 174 (35·8%) |
| Anaemia | 92 (18·9%) | 34 (7·0%) | 4 (0·8%) | 1 (0·2%) |
| Febrile neutropenia | 2 (0·4%) | 2 (0·4%) | 17 (3·5%) | 13 (2·7%) |
| Thrombocytopenia | 14 (2·9%) | 1 (0·2%) | 0 | 1 (0·2%) |
| **Non-haematological** | | | | |
| Fatigue | 161 (33·1%) | 102 (21·0%) | 21 (4·3%) | 0 |
| Nausea | 164 (33·7%) | 48 (9·9%) | 5 (1·0%) | 0 |
| Diarrhoea | 125 (25·7%) | 45 (9·3%) | 15 (3·1%) | 1 (0·2%) |
| Rash | 57 (11·7%) | 41 (8·4%) | 6 (1·2%) | 0 |
| Neuropathy | 88 (18·1%) | 8 (1·6%) | 3 (0·6%) | 0 |
| Constipation | 62 (12·8%) | 27 (5·6%) | 1 (0·2%) | 0 |
| Oedema | 72 (14·8%) | 12 (2·5%) | 2 (0·4%) | 0 |
| Myalgia | 50 (10·3%) | 27 (5·6%) | 4 (0·8%) | 0 |
| Arthralgia | 37 (7·6%) | 25 (5·1%) | 4 (0·8%) | 0 |
| Pain | 40 (8·2%) | 20 (4·1%) | 4 (0·8%) | 0 |
| Mucositis | 56 (11·5%) | 31 (6·4%) | 3 (0·6%) | 0 |
| Anorexia | 47 (9·7%) | 8 (1·6%) | 1 (0·2%) | 0 |
| Headache | 36 (7·4%) | 14 (2·9%) | 5 (1·0%) | 0 |
| Hot flushes | 34 (7·0%) | 15 (3·1%) | 1 (0·2%) | 0 |
| Fever | 37 (7·6%) | 4 (0·8%) | 2 (0·4%) | 3 (0·6%) |
| Vomiting | 31 (6·4%) | 12 (2·5%) | 3 (0·6%) | 0 |
| Shortness of breath | 32 (6·6%) | 3 (0·6%) | 5 (1·0%) | 1 (0·2%) |
| Cardiac dysfunction | 12 (2·5%) | 15 (3·1%) | 2 (0·4%) | 0 |

Data are n (%). *Safety population included all patients who received at least one dose of study drug.

***Table 3:*** **Treatment-related adverse events in the safety population* (n=486) by grade**

## Discussion

Our findings show that a short, four cycle, non-anthracycline-based adjuvant chemotherapy regimen of docetaxel and cyclophosphamide, combined with trastuzumab, could be effective for women with

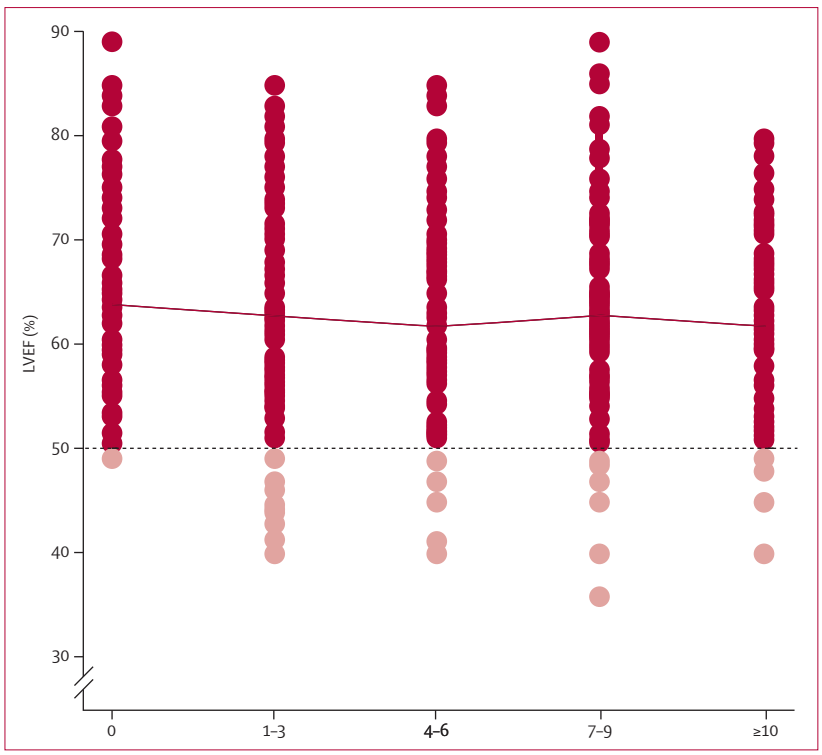


*Figure 2:* **Left ventricular ejection fraction data over time for the 486 patients who received at least one dose of study drug**

| | N | Median (range) |
|---|---|---|
| Baseline | 486 | 64·0% (49·0–89·0) |
| 1–3 months | 455 | 63·0% (40·0–85·0) |
| 4–6 months | 430 | 62·0% (40·0–85·0) |
| 7–9 months | 416 | 62·8% (36·0–89·0) |
| ≥10 months | 372 | 62·0% (40·0–80·0) |

*Table 4:* **Change in left ventricular ejection fraction by month**

*HER2*-amplified early breast cancer, irrespective of *TOP2A* status. The 3-year DFS of 96·9% identified in this phase 2 study compares favourably with other reports,[21–23] particularly in the node-negative population. Anthracyclines have been the treatment of choice since 1990, when the National Surgical Adjuvant Breast and Bowel Project B-15 study showed that four cycles completed in 12 weeks was as effective as the standard treatment regimen of cyclophosphamide, methotrexate, and fluorouracil.[23] However, anthracyclines can cause cardiotoxicity and bone marrow dysfunction.[24] Adjuvant trastuzumab has been shown to improve outcomes in patients with *HER2*-amplified breast cancer, but also has the potential for cardiotoxicity.[24–26] When trastuzumab is combined with an anthracycline-based regimen, cardiac dysfunction, and bone marrow damage are increased.[8,24–27] Studies have confirmed that non-anthracycline regimens used in the adjuvant setting can be as effective as anthracyclines in some other settings.[8,26] Non-anthracycline docetaxel plus cyclophosphamide has been shown to be effective in treatment of patients with early stage breast cancer in general.[26] In the present study, we extend that finding to the *HER2*-amplified population with the addition of trastuzumab to docetaxel plus cyclophosphamide.

We selected short-term follow-up for this trial because most recurrences in HER-amplified cancers happen in this timeframe.[21–24] We recognise that recurrences can happen after 3 years, but the 3-year DFS is consistent with other reports such as those from the BCIRG 006 trial.[13] Stopping rules were not planned in this trial because fewer cardiac toxic effects were expected with docetaxel, cyclophosphamide, and trastuzumab than with anthracycline regimens . By contrast with anthracyclines,[11,28] no relation between efficacy and *TOP2A* gene copy number was shown for our regimen, but this finding is not surprising with a non-anthracycline regimen. Similarly, we identified no relation between *c-MYC* gene copy number and outcome.

***Panel:* Research in Context**

**Systematic review**

We searched PubMed from May 1, 2005, to Aug 18, 2013, with the key words "adjuvant", "trastuzumab", and "early HER2-positive breast cancer". At the time of planning the trial, four major randomised trials of chemotherapy with or without trastuzumab,[21–24] had been reported. In a retrospective analysis by *HER2* status, docetaxel plus cyclophosphamide seemed to be superior to doxorubicin plus cyclophosphamide in patients with *HER2*-amplified early stage breast cancer. In all the major randomised studies, only about 1000 patients received a non-anthracycline regimen and relatively few patients with lower risk, node-negative disease were included. Trastuzumab has been shown to be effective in combination with anthracycline-based adjuvant regimens, but is cardiotoxic. Thus, we did a single-group phase 2 study of lower risk patients with *HER2*-amplified early stage breast cancer to assess the efficacy and safety of docetaxel and cyclophosphamide plus trastuzumab.

**Interpretation**

Our data are promising up to 3-years of follow-up, with results being consistent with the those obtained using much longer-duration chemotherapy regimens as reported in the major randomised trials. Additionally, we included 95 patients with node-negative cancers and tumours 1 cm or smaller in size and showed a 100% disease-free survival at 3 years. Prospective data for such patients were, to the best of our knowledge, not available previously. Thus, a short regimen of four cycles of docetaxel and cyclophosphamide combined with 1 year of trastuzumab could be an option for many women with lower risk *HER2*-amplified early stage breast cancer, irrespective of *TOP2A* status.

Docetaxel and cyclophosphamide given as four cycles of chemotherapy in conjunction with trastuzumab results in a shorter duration of chemotherapy than with most other approved regimens, such as doxorubicin and paclitaxel followed by cyclophosphamide plus docetaxel[24,29] or docetaxel and carboplatin plus trastuzumab.[25] Slamon and colleagues[24] administered docetaxel, carboplatin, and trastuzumab for six cycles and showed a 5-year DFS of 81% and overall survival of 91% in all patients; in the node-negative group 5-year DFS was 93% for doxorubicin, cyclophoshamide, docetaxel, and trastuzumab, and 90% for docetaxel, carboplatin, and trastuzumab. Our results compare favourably with these findings.

Our study included 95 women with small cancers (<1·0 cm) and negative nodes, who had 100% DFS at 3 years. Comparable data for this group do not exist because such patients have generally been excluded from previous trials.[21–23] Whether chemotherapy is even necessary for this group when treated with trastuzumab is a topic for future study (panel).

Trastuzumab is cardiotoxic, particularly in combination with anthracyclines.[26] However, we found that trastuzumab combined with four cycles of docetaxel plus cyclophosphamide caused mainly asymptomatic decreases in LVEF. Around 5% of patients who received at least one dose of study drug exhibited a decrease in LVEF to less than 50% at some point during the study. Almost a quarter of patients had a decrease of 10% in LVEF at some point in the study, and one patient had congestive heart failure. Other cardiac events were rare.

Some limitations of our study are the small size, the lack of a control arm, and the emphasis on lower risk (node-negative) *HER2*-amplified early stage breast cancer.

We conclude that four cycles of docetaxel, cyclophosphamide, and trastuzumab could be a reasonable alternative to the six-cycle regimen studied by Slamon and colleagues[24] in lower risk node-negative patients with early stage breast cancer, particularly those with subcentimetre disease. Additional studies would be helpful to confirm these results in a larger population of patients; for example, a randomised study of docetaxel, cyclophosphamide, and trastuzumab could be compared with trastuzumab alone.

#### Contributors

SEJ contributed to study design, scientific literature search, data analysis, data interpretation, and writing and final approval of the report. RC, DLL, MAKA, MSS, and CS enrolled patients on the study and contributed to data collection and final approval of the report. DP, AMF, BDB, RMP, and NJR enrolled patients on the study and reviewed final report. SS enrolled patients and contributed to data collection and review of the final report. IG, SJV, and MWC contributed to data collection and final approval of the report. FAH enrolled patients, made suggestions for the report and contributed to the final review of the report. YW and LA contributed to statistical analysis, figures, and writing and final approval of the report. JO'S contributed to study design, data analysis, data interpretation, and writing and final approval of the report.

#### Conflicts of interest

SEJ has been a speaker for Sanofi and currently is a speaker for Genentech. FAH is a speaker for Genentech. NJR is a consultant for Sanofi. JO'S is a consultant for Sanofi. The other authors declare that they have no conflicts of interest.

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