Original Article

# Multicenter study of primary systemic therapy with docetaxel, cyclophosphamide and trastuzumab for HER2-positive operable breast cancer: the JBCRG-10 study

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## Abstract

**Background:** The original aim of this study was to evaluate the treatment sequence and anthracycline requirement in docetaxel, cyclophosphamide and trastuzumab therapy. After one death in the anthracycline-containing arm, the protocol was amended to terminate the randomization. The single-docetaxel, cyclophosphamide and trastuzumab arm was continued to examine the efficacy and safety of the anthracycline-free regimen.

**Methods:** Women with human epidermal growth factor receptor-2-positive, operable and primary breast cancer were randomized to receive 5-fluorouracil, epirubicin and cyclophosphamide (four cycles) followed by docetaxel, cyclophosphamide and trastuzumab (four cycles), or docetaxel, cyclophosphamide and trastuzumab followed by 5-fluorouracil, epirubicin and cyclophosphamide, or docetaxel, cyclophosphamide and trastuzumab (six cycles). After the protocol amendment, patients were allocated to the docetaxel, cyclophosphamide and trastuzumab arm alone. The primary endpoint was a pathological complete response.

**Results:** In total, 103 patients were enrolled between September 2009 and September 2011: 21, 22 and 24 patients in the 5-fluorouracil, epirubicin and cyclophosphamide followed by docetaxel, cyclophosphamide and trastuzumab; docetaxel, cyclophosphamide and trastuzumab followed by 5-fluorouracil, epirubicin and cyclophosphamide and docetaxel, cyclophosphamide and trastuzumab arms, respectively, and 36 patients in the docetaxel, cyclophosphamide and

trastuzumab arm after the protocol amendment. In total, 60 patients were allocated to the docetaxel, cyclophosphamide and trastuzumab arm, in which the pathological complete response rate was 45.8%, and disease-free survival at 3 years was 96.6%. Patients with stage I or IIA in the docetaxel, cyclophosphamide and trastuzumab arm showed good disease-free survival (100% at 3 years). The comparison of efficacy among the three arms was statistically underpowered. Left ventricular ejection fraction decreased significantly after 5-fluorouracil, epirubicin and cyclophosphamide followed by docetaxel–docetaxel, cyclophosphamide and trastuzumab ($P = 0.017$), but not after docetaxel, cyclophosphamide and trastuzumab followed by 5-fluorouracil, epirubicin and cyclophosphamide or docetaxel, cyclophosphamide and trastuzumab.

**Conclusions:** The pathological complete response rate for docetaxel, cyclophosphamide and trastuzumab was similar to previous reports of anthracycline-containing regimens. Docetaxel, cyclophosphamide and trastuzumab might be an option for primary systemic therapy in human epidermal growth factor receptor-2-positive early breast cancer. A larger confirmatory study is necessary.

## Introduction

The current standard primary systemic therapy (PST) for human epidermal growth factor receptor-2 (HER2)-positive breast cancer is anthracyclines and/or taxanes combined with anti-HER2 antibodies including trastuzumab and pertuzumab, which demonstrates a high pathological complete response (pCR) rate [1–5]. pCR is considered a predictive marker of prognosis in patients with HER2-positive breast cancer, although its usefulness differs depending on hormone receptor status [1, 6, 7]. In patients whose tumors do not achieve pCR after PST, adjuvant use of trastuzumab emtansine has been shown to further reduce recurrence risk [8]. PST is, therefore, a practical strategy to improve the outcome of patients with HER2-positive breast cancer.

The addition of pertuzumab to trastuzumab-containing chemotherapy has been shown to improve the pCR rate in the neoadjuvant setting and invasive disease-free survival (DFS) in the adjuvant setting, although the survival gain at 3 years is not large [4, 5, 9]. Thus, it is critical to select patients with HER2-positive breast cancer who need pertuzumab in the neoadjuvant or adjuvant setting. To this end, it is clinically important to identify those patients who have a favorable prognosis with a trastuzumab-containing regimen without pertuzumab.

The combination of docetaxel, cyclophosphamide, and trastuzumab (TCH) has been studied in the adjuvant and neoadjuvant settings [10, 11]. The combination therapy gave a good outcome with 2-year DFS of 97.8% as adjuvant therapy in patients with stage I–III breast cancer [10]. It also gave a good pCR rate of 43.9% in a similar population [11]. However, several clinical questions remain, including the additional effect of anthracycline combined with TCH to improve the outcome; the preferred order of anthracycline and taxane; the effect and safety of anthracycline-free regimens and the population with a good prognosis with anthracycline-free regimens.

This study was originally designed to investigate different sequences of treatment as follows: 5-fluorouracil (5FU), epirubicin and cyclophosphamide (CPA) (FEC) followed by TCH (FEC-TCH); TCH-FEC; and TCH regimens. Because of one death from interstitial lung disease (ILD) after the completion of eight cycles in the FEC-TCH arm, an unplanned interim analysis was conducted, which

suggested that anthracycline-containing regimens did not have benefits over the TCH regimen. Thus, a protocol amendment was made to discontinue randomization in consideration of the efficacy and safety of the treatment. The study continued thereafter with the allocation of enrolled patients to the TCH arm alone in order to examine the efficacy and safety of the anthracycline-free regimen.

## Methods

### Patients

This study involved treatment-naïve women with operable HER2-positive (IHC 3+ or FISH+) invasive breast cancer diagnosed histologically by core needle biopsies. Eligible patients were those who had a primary tumor $\leq 7$ cm in diameter as assessed by physical examination; were classified as having tumor stage T1c to T3, nodal stage $\leq$ N1 and metastasis stage M0; were aged between 20 and 70 years; had an Eastern Cooperative Oncology Group performance status score of 0 or 1; had a baseline left ventricular ejection fraction (LVEF) $\geq 55\%$ on echocardiography or multigated acquisition scan; and did not have QTc prolongation on electrocardiogram. In addition, no evident ILD on the baseline chest computed tomography (CT) imaging was required for eligibility.

### Study oversight

The protocol was approved by the ethics review committee of the Japan Breast Cancer Research Group (JBCRG) and then by each institutional review board. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before participating in the study.

### Study design and treatment plan

This was a multicenter, open-label, randomized, phase II study. Eligible patients were randomly assigned to one of three neoadjuvant chemotherapy regimens: FEC-TCH [four cycles of 5FU (500 mg/m$^2$, q3w) + epirubicin (100 mg/m$^2$, q3w) + CPA (500 mg/m$^2$, q3w) followed by four cycles of docetaxel (75 mg/m$^2$, q3w) + CPA (600 mg/m$^2$, q3w) + trastuzumab (2 mg/kg, weekly with loading
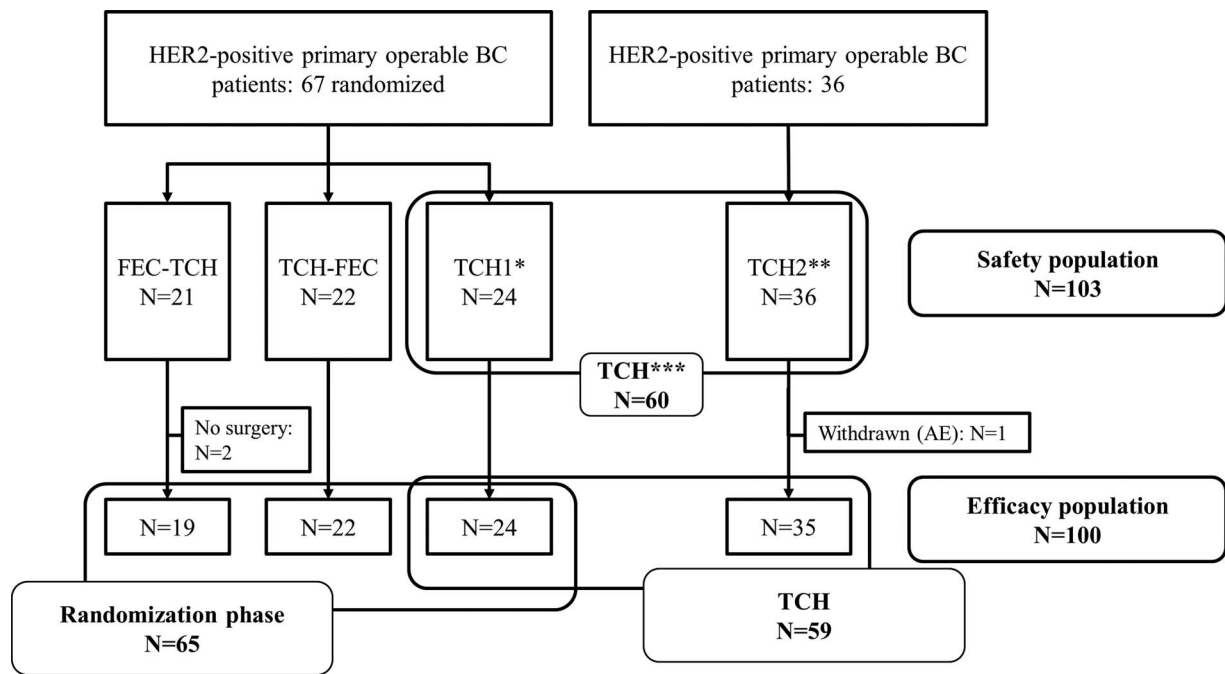
*Before interim analysis (randomization phase), **After interim analysis (non-randomization phase)
***Total number of patients treated with TCH

**Figure 1.** Patient disposition. 'TCH1' was defined as the population of patients in the randomization phase, 'TCH2' was defined as the patient population enrolled after the interim analysis and 'TCH' referred to the total population treated with TCH. HER2, human epidermal growth factor receptor-2; BC, breast cancer; PD, progressive disease; AE, adverse event; FEC, 5FU + epirubicin + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab.

4 mg/kg, or 6 mg/kg, q3w with loading 8 mg/kg)], TCH-FEC (four cycles of TCH followed by four cycles of FEC), or six cycles of TCH. Patients were stratified according to age (<50 years versus ≥50 years), nodal status (N0 versus N1), estrogen receptor (ER) status (positive versus negative) and study site. After the protocol amendment, patients were allocated to the TCH arm alone. The addition of anthracycline-based therapy as adjuvant therapy was considered for patients in the TCH arm whose tumor showed non-pCR based on postoperative results.

### Study endpoints

The primary endpoint was the pCR rate, defined as no evidence of residual invasive tumor in the breast, irrespective of ductal carcinoma *in situ* (ypT0/is). Secondary endpoints included safety (CTCAE v3.0) [12], the cardiac toxicity rate, the overall response rate evaluated by magnetic resonance imaging/CT (RECIST v1.1) [13], the breast-conservation rate, the lymph node dissection rate, DFS and overall survival (OS).

### Statistical analysis

This study was planned using the randomized selection phase II design by Simon et al. [14]. The primary objective of this study was to compare the pCR rate among the three arms. The expected baseline pCR rate in this study was set at 40%, and an increase in the pCR rate by 15% was considered to demonstrate clinical usefulness. Therefore, with the assumption that the probability of correctly selecting an arm with a high pCR rate is ≥90%, a sample size of 180 patients was determined, consisting of 60 patients in each arm, with consideration for dropouts of ∼10%. After the protocol amendment, the randomization was discontinued and enrolled patients were

allocated to the TCH arm until 60 patients were enrolled in the TCH arm in total. DFS and OS were estimated using the Kaplan–Meier method and log-rank test. Left LVEF was compared by Dunnett-type multiple comparisons. A two-sided $P$ value < 0.05 was considered significant. All statistical analyses were performed by JMP ver. 13.2.0 (SAS Institute Japan, Tokyo).

## Results

### Baseline characteristics

Between September 2009 and September 2011, 103 patients were enrolled from 15 institutions (Fig. 1). All patients were evaluable for safety (safety population, full analysis set). An unplanned interim analysis was conducted because of one death from ILD in the FEC-TCH group after the completion of eight cycles. The interim analysis suggested that anthracycline-containing regimens did not have benefits over the TCH regimen in terms of the pCR rate while toxicity with anthracycline and eight cycles of CPA was a concern. In addition, the possibility of anthracycline-free regimen had been vigorously investigated at the time. Thus, the decision was made that the randomization was discontinued to close the two anthracycline-containing arms and the study continued thereafter with the allocation of enrolled patients to the TCH arm alone. The eligibility after the amendment was consistent. 'TCH1' was defined as the population of patients in the randomization phase, 'TCH2' was defined as the patient population enrolled after the interim analysis, and 'TCH' referred to the total population treated with TCH (patients in and after the randomization phase combined) (Fig. 1).

**Table 1.** Baseline patient characteristics

| | TCH | Randomization phase | | |
| --- | --- | --- | --- | --- |
| Characteristic | TCH (N = 60) | FEC-TCH (N = 21) | TCH-FEC (N = 22) | TCH1 (N = 24) |
| Age at enrollment (year) | | | | |
|   Median (range) | 54.5 (33–67) | 53 (38–70) | 52 (36–62) | 55.5 (34–66) |
| Menopausal status [no. (%)] | | | | |
|   Premenopausal | 22 (36.7) | 10 (47.6) | 10 (45.5) | 9 (37.5) |
|   Postmenopausal | 38 (63.3) | 11 (52.4) | 12 (54.5) | 15 (62.5) |
| Tumor size at diagnosis [no./total no. (%)] | | | | |
|   Median (range, mm) | 35.5 (3–80) | 35 (15–80) | 31 (3–58) | 40 (14–70) |
|   T1 (≤2 cm) | 6 (10.0) | 2 (9.5) | 0 (0.0) | 4 (16.7) |
|   T2 (>2–≤5 cm) | 49 (81.7) | 16 (76.2) | 18 (81.8) | 18 (75.0) |
|   T3 (>5 cm) | 5 (8.3) | 3 (14.3) | 4 (18.2) | 2 (8.3) |
| Nodal status | | | | |
|   N0 | 35 (58.3) | 13 (61.9) | 13 (59.1) | 16 (66.7) |
|   N1 | 25 (41.7) | 8 (38.1) | 9 (40.9) | 8 (33.3) |
| Hormone receptor status [no. (%)] | | | | |
|   ER-positive and/or PgR-positive | 34 (56.7) | 14 (66.7) | 14 (63.6) | 12 (50.0) |
|   ER-negative and PgR-negative | 26 (43.3) | 7 (33.3) | 8 (36.4) | 12 (50.0) |
| HER2 status [no. (%)] | | | | |
|   IHC (3+) | 57 (95.0) | 18 (85.7) | 20 (90.9) | 23 (95.8) |
|   IHC (2+) and FISH (+) | 2 (3.3) | 1 (4.8) | 1 (4.5) | 1 (4.2) |
|   IHC (unknown) and FISH (+) | 1 (1.7) | 2 (9.5) | 1 (4.5) | 0 (0.0) |
| Histological grade [no. (%)] | | | | |
|   1 | 3 (5.0) | 0 (0.0) | 3 (13.6) | 2 (8.3) |
|   2 | 9 (15.0) | 5 (23.8) | 4 (18.2) | 4 (16.7) |
|   3 | 32 (53.3) | 13 (61.9) | 13 (59.1) | 14 (58.3) |
|   unknown | 16 (26.7) | 3 (14.3) | 2 (9.1) | 4 (16.7) |
| Type of surgery planned | | | | |
|   Breast-conserving | 33 (55.0) | 9 (42.9) | 13 (59.1) | 14 (58.3) |
|   Mastectomy | 27 (45.0) | 12 (57.1) | 9 (40.9) | 10 (41.7) |
| Baseline LVEF (%) | | | | |
|   Median (range) | 70 (59.6–82.9) | 71 (55–76.9) | 71 (60–80) | 71.5 (62–82.9) |

Balancing adjustment factors for randomization using a minimization method were ER status (positive/negative), age (≤50 years), axillary lymph node metastasis (No/N1) and institution.

HER2, human epidermal growth factor receptor-2; FEC, 5FU + epirubicin + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab; LVEF, left ventricular ejection fraction; ER, estrogen receptor; PgR, progesterone receptor.

The median patient age was 54 years (range, 33–70 years), the median tumor size was 35 mm (range, 12–80 mm), 42 patients had the node-positive disease (40.8%) and 62 patients had ER-positive disease (60.2%). Characteristics of patients in the TCH, FEC-TCH, TCH-FEC and TCH1 treatment arms are shown in Table 1.

### Efficacy
Efficacy assessment was performed in 100 patients (Fig. 1) because one patient in the FEC-TCH arm died of ILD as mentioned above, one died of an unknown cause just after the first cycle of FEC-TCH and one was withdrawn due to a severe adverse event (vomiting and diarrhea) after the first cycle of TCH. Efficacy analyses were first performed in the TCH population, and then exploratory analyses were conducted of the three groups in the randomization phase.

### TCH
*Response.* The breast pCR (ypT0/is) rate was 46% in the TCH arm (n = 59) (Table 2). The breast and nodal pCR rate (ypT0/is + ypN0) was 42% (25/59 patients), and 5 of 34 patients with non-pCR

(ypT0/is + ypN0) received postoperative chemotherapy including anthracycline. Breast pCR (ypT0/is) rates by ER status were 33.3% (11/33) in ER-positive patients and 61.6% (16/26) in ER-negative patients; the difference in the pCR rate was significant (P = 0.03).

The overall response rate was 86% [95% CI: 77–96] (Table 3). The breast-conservation rate was 59%, and the proportion of patients who had been planned for mastectomy before PST but received breast-conserving surgery was 33% (9/27 patients).

### Survival
The median length of follow-up was 36.5 months (range, 6–60 months). DFS and OS at 3 years were 96.6% and 98.3%, respectively (Fig. 2a and b). No significant difference was observed in DFS between the pCR (ypT0/is) and non-pCR groups (P = 0.87; Fig. 2c). ER status was not significantly associated with DFS (P = 0.83; Fig. 2d). The clinical stage at baseline was associated with DFS; patients with stages I and IIA showed a good prognosis, with 3-year DFS of 100% (P = 0.0004; Fig. 2e).

FEC-TCH, TCH-FEC and TCH1 in the randomization phase: exploratory analyses.
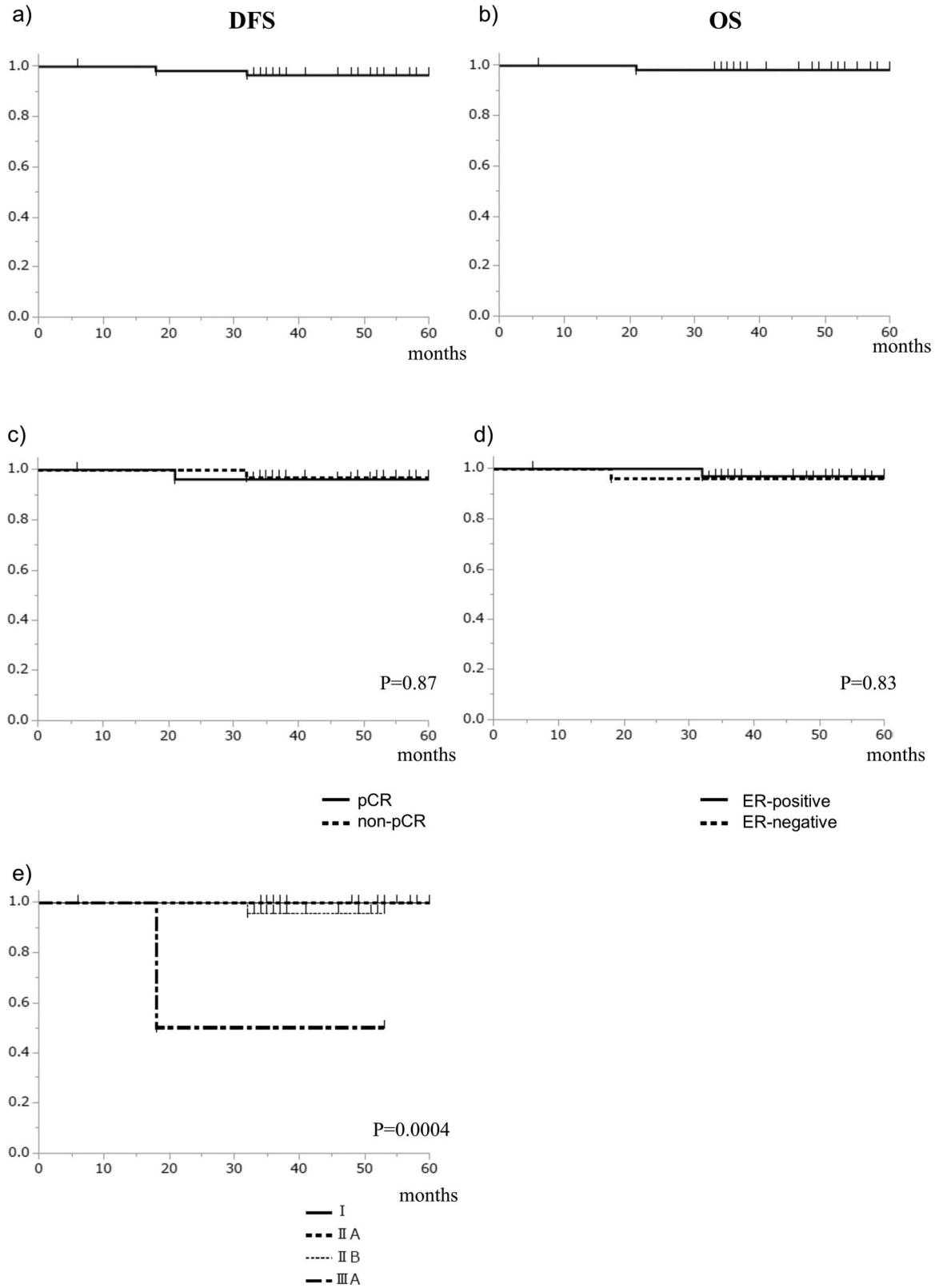
**Figure 2.** Survival analysis in the TCH arm. Disease-free survival (DFS) (a) and overall survival (OS) (b) in the TCH arm, and DFS by pCR status (c), ER status (d) and clinical stage (e) in the TCH arm. pCR, pathological complete response; ER, estrogen receptor; FEC, 5FU + epirubicin + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab.

**Table 2**. Pathological response

|  | TCH | Randomization phase (N = 65) | | | |
|---|---|---|---|---|---|
|  | TCH (N = 59) | FEC-TCH (N = 19) | TCH-FEC (N = 22) | TCH1 (N = 24) | Comparative *P* value across three groups |
| ypT0/is | 45.8 (33.7–58.3) | 42.1 (23.1–63.7) | 36.4 (19.7–57.0) | 54.2 (35.1–72.1) | 0.46 |
| ypT0 | 30.5 (20.3–43.1) | 31.6 (15.4–54.0) | 22.7 (10.1–43.4) | 33.3 (18.0–53.3) | 0.70 |
| ypT0/is +ypN0 | 42.3 (30.6–55.1) | 36.8 (19.1–59.0) | 36.4 (19.7–57.0) | 54.2 (35.1–72.1) | 0.39 |

Values are for pCR in breast and/or lymph nodes (%, 95% CI).

FEC, 5FU + epirubicin + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab.

**Table 3**. Overall clinical response and surgical procedures (planned → performed)

|  | TCH | Randomization phase (N = 65) | | |
|---|---|---|---|---|
|  | TCH (N = 59) | FEC-TCH (N = 19) | TCH-FEC (N = 22) | TCH1 (N = 24) |
| Overall response rate (95% confidence interval) | 86 (77–96) | 95 (83–100) | 77 (57–97)) | 83 (66–100) |
| CR, *n* (%) | 20 (34) | 11 (58) | 10 (46) | 14 (58) |
| PR, *n* (%) | 31 (53) | 7 (37) | 7 (32) | 7 (37) |
| SD, *n* (%) | 7 (12) | 1 (5) | 4 (18) | 1 (5) |
| PD, *n* (%) | 1 (1) | 0 (0) | 1 (4) | 0 (0) |
| Breast-conserving rate, % (*n*) | 59 (35/59) | 68 (13/19) | 77 (17/22) | 63 (15/24) |
| Mastectomy changed to breast-conserving surgery[a], % (*n*) | 33 (9/27) | 40 (4/10) | 44 (4/9) | 40 (4/10) |

[a]Breast-conserving rate for patients whose mastectomy had been required by their physicians in the diagnoses before initiation of neoadjuvant chemotherapy.

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FEC, 5FU + epirubicin + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab.

*Response.* Breast pCR (ypT0/is) rates were 42%, 36% and 54% in the FEC-TCH (*n* = 19), TCH-FEC (*n* = 22) and TCH1 (*n* = 24) arms, respectively (Table 2). Breast and nodal pCR rates (ypT0/is + ypN0) were 37%, 36% and 54%, respectively.

The overall response rate was 95% [95% CI: 83–100] in the FEC-TCH arm, 77% [95% CI: 57–97] in the TCH-FEC arm and 83% [95% CI: 66–100] in the TCH1 arm (Table 3); breast-conservation rates were 68%, 77% and 63%, respectively. The proportion of patients who had been planned for mastectomy before PST but received breast-conserving surgery were 40% (4/10 patients) in the FEC-TCH arm, 44% (4/9 patients) in the TCH-FEC arm and 40% (4/10 patients) in the TCH1 arm.

*Survival.* The median length of follow-up was 53 months (range, 6–62 months). DFS was similar among the three groups: 100% in the FEC-TCH arm, 95.5% in the TCH-FEC arm and 95.7% in the TCH1 arm at 3 years (*P* = 0.77; Fig. 3a). Similar results for OS were observed: 100% in the FEC-TCH arm, 100% in the TCH-FEC arm and 95.7% in the TCH1 arm at 3 years (*P* = 0.57; Fig. 3b).

*Safety*

**TCH**   Safety was evaluated in 60 patients in the TCH arm (Table 4). Overall, grade 3 or higher toxicity was seen in 45% in the TCH arm. Leucopenia and febrile neutropenia were the most frequently reported grade 3 or higher adverse events. ILD at any grade was reported in four patients, which resolved in all patients. No grade 3/4 ILD was observed. The LVEF dropped from 70.5% ± 0.6% (mean ± SE) to 68.1% ± 0.7% at four cycles (*P* = 0.020), but it recovered to 69.5% ± 0.7% after six cycles (*P* = 0.46) (Fig. 4).

**FEC-TCH, TCH-FEC and TCH1 in the randomization phase**   Safety was evaluated in 67 patients in the randomization phase (Table 4). Overall, grade 3 or higher toxicity was seen in 67% of patients undergoing FEC-TCH, 45% in the TCH-FEC arm and 46% in the TCH1 arm. Commonly reported grade 3 or higher adverse events were leucopenia and febrile neutropenia. ILD was reported in five patients (FEC-TCH: *n* = 1; TCH-FEC: *n* = 1; TCH1: *n* = 3), which resolved in all patients but one in the FEC-TCH arm. One patient was diagnosed with grade 3 heart failure in the FEC-TCH arm. The LVEF after the whole treatment course changed from 70.8% ± 0.8% to 66.5% ± 1.2% in the FEC-TCH arm, 71.5% ± 1.0% to 70.3% ± 0.8% in the TCH-FEC arm and 71.7% ± 1.0% to 69.9% ± 0.9% in the TCH1 arm. The reduction in LVEF was significant in the FEC-TCH arm (*P* = 0.017), but not in the TCH-FEC arm or the TCH1 arm (Fig. 4). In the TCH1 arm, LVEF dropped from 71.7% ± 1.0% to 68.3% ± 1.0% at four cycles (*P* = 0.039), but it recovered after six cycles (*P* = 0.31).

**Discussion**

This study was originally conducted in patients with operable HER2-positive breast cancer to examine the efficacy and safety of regimens administered in different sequences (an anthracycline-first regimen and a taxane-first regimen), and also to examine the efficacy and safety of regimens with or without anthracycline. However, because one patient died of ILD in the FEC-TCH arm during the course of the study, an interim analysis was performed to evaluate whether the study should be continued. The independent data monitoring committee concluded that no further improvement in efficacy was to be expected in terms of pCR in the FEC-TCH and TCH-FEC arms. On the other hand, toxicity with anthracycline and eight cycles
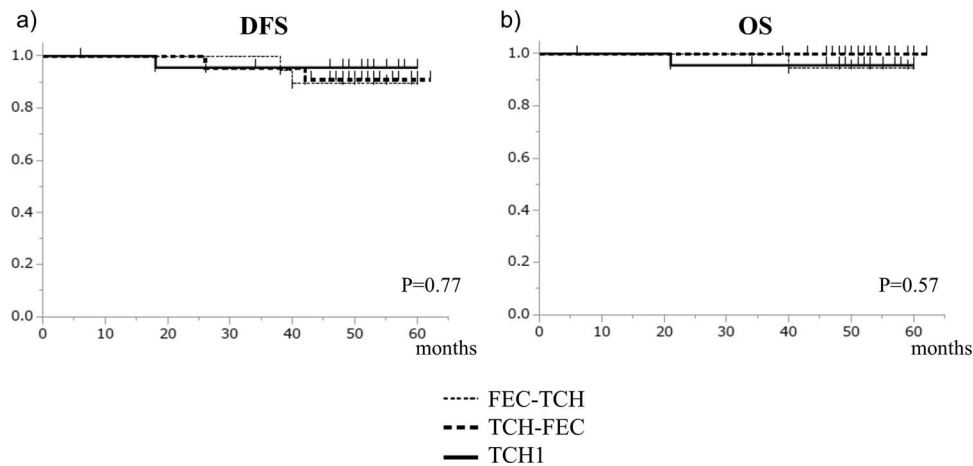
**Figure 3.** Survival analysis in the randomization phase. Disease-free survival (DFS) (a) and overall survival (OS) (b) among three arms in the randomization phase. FEC, 5FU + epirubicin + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab.

**Table 4.** Grade 3/4 adverse events.

| | TCH | Randomization phase ($N = 67$) | | |
|---|---|---|---|---|
| | TCH ($N = 60$) $n$ (%) | FEC-TCH ($N = 21$) $n$ (%) | TCH-FEC ($N = 22$) $n$ (%) | TCH1 ($N = 24$) $n$ (%) |
| White blood cell count decreased | 8 (13) | 1 (5) | 3 (14) | 4 (17) |
| Neutropenia | 8 (13) | 4 (19) | 3(14) | 4 (17) |
| Febrile neutropenia | 14 (23) | 4 (19) | 7 (32) | 4 (17) |
| Neutropenia (grade 3/4) with infection | 3 (5) | – | 1 (5) | 1 (4) |
| Liver dysfunction (increased AST and/or ALT) | 1(2) | – | 1(5) | 1(4) |
| Vomiting | – | 2 (10) | – | – |
| Diarrhea | 1 (2) | – | – | – |
| Fatigue (asthenia/lethargic/malaise) | 1 (2) | – | – | – |
| Pulmonary embolism[a] | – | 1 (5) | – | – |
| Interstitial lung disease | – | 1 (5) | – | – |
| Heart failure | | 1 (5) | | |
| Nail changes | 1 (2) | – | – | – |
| Rash/desquamation | 1 (2) | – | – | 1 (4) |
| Herpes zoster/herpes | – | – | 1(5) | – |
| Edema (extremities) | 1 (2) | – | – | – |
| Total | 27 (45) | 14 (67) | 10 (45) | 11 (46) |

[a]Deep vein thrombosis was also reported in the same patient.

of CPA raised concerns. In addition, regimens without anthracycline had been clinically desired. The study continued thereafter with the allocation of enrolled patients to the TCH arm alone. Accordingly, it became impossible to perform the planned comparison of efficacy by the sequence of administration in the present study. In a crossover study (15), it was reported that clinical efficacy was similar between anthracycline-first and taxane-first regimens used as first-line treatments for patients with metastatic breast cancer. Following this study, the efficacy and safety of PST were assessed using FEC-docetaxel (DTX) therapy (FEC followed by DTX) in JBCRG 01 (16) and DTX-FEC therapy, in a reverse sequence, in JBCRG 03 (6). The pCR rates in these two studies were similar (25% and 23%, respectively). The present study showed a consistent result (Table 2), although it was statistically underpowered to confirm the result.

The efficacy of the anthracycline-free TCH regimen in the present study seems comparable to the efficacies of the anthracycline-containing regimens in other previous studies in terms of the pCR rate (1–3). In addition, the present results were consistent with previously reported studies on TCH in the neoadjuvant and adjuvant settings (10, 11). Furthermore, patients with stage I and IIA breast cancer showed a good prognosis with the TCH regimen alone (Fig. 2e) in the present study, suggesting that TCH could be an option for perioperative systemic treatment of HER2-positive breast cancer, especially for early-stage disease. Caution is needed because the previous studies used four cycles of TCH instead of six cycles (10, 11). Thus, further studies are necessary to determine the optimal cycle number of TCH as neoadjuvant and adjuvant chemotherapy for HER2-positive breast cancer.

A number of studies have been examining regimens with less toxicity and similar or greater efficacy for HER2-positive breast cancer. Addition of anti-HER2 therapies such as lapatinib and pertuzumab has been tested and shown to give good pathological responses. In NeoALTTO trial, the addition of lapatinib onto paclitaxel plus trastuzumab gave a pCR rate of 51.3% (17). Similarly, CALGB40601 study gave a pCR rate of 56% with the combination of lapatinib with paclitaxel and trastuzumab (18). In NeoSphere trial, the addi-
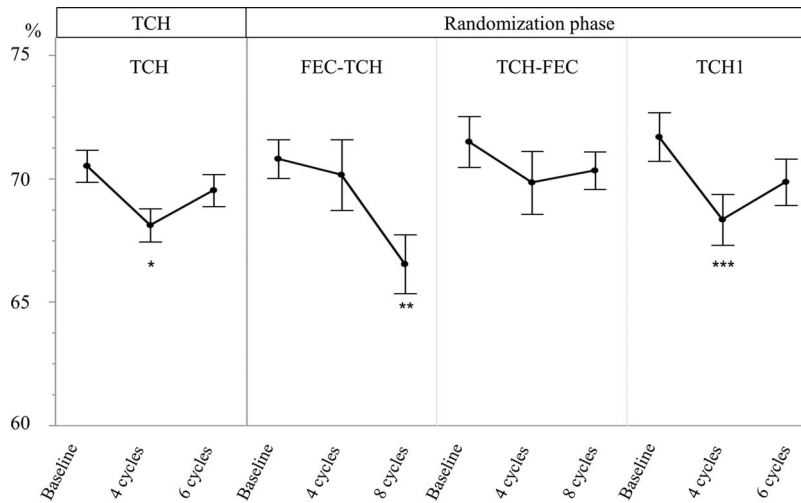
**Figure 4.** Mean change in left ventricular ejection fraction (LVEF) from baseline (mean ± SE). The decrease in LVEF was significant after four cycles in the TCH arm (*N* = 60; *P* = 0.020) but disappeared after the whole treatment. In the randomization phase, LVEF significantly decreased after the whole treatment in the FEC-TCH arm (*N* = 21; *P* = 0.017) but not in the TCH-FEC arm (*N* = 22) or the TCH1 arm (*N* = 24). LVEF dropped at four cycles in the TCH1 arm (*P* = 0.039) but recovered after six cycles. LVEF was compared by Dunnett-type multiple comparisons with baseline as control. \**P* = 0.020; \*\**P* = 0.017; \*\*\**P* = 0.039. FEC, 5FU + epirubicin + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab; SE, standard error.

tion of pertuzumab onto docetaxel plus trastuzumab gave a pCR rate of 45.8% (4). Although these studies gave or recommended anthracycline-containing regimens after surgery, high pCR rates in the neoadjuvant phase suggest possible treatment strategies without anthracycline. Indeed, in TRAIN-2 trial, nine cycles of paclitaxel and carboplatin with trastuzumab plus pertuzumab gave a pCR rate of 68%, which was comparable with the anthracycline-containing arm (19). In this context, it will be of clinical value to test a combination of pertuzumab with TCH regimen to further improve the efficacy of the combination. Addition of immune checkpoint inhibitors is another promising strategy. In metastatic settings, the combination of pembrolizumab and trastuzumab showed durable clinical benefit in patients with PD-L1-positive, trastuzumab-resistant breast cancer, suggesting an additional benefit of immune checkpoint inhibitors onto anti-HER2 therapies (20).

In the present study, LVEF did not show a significant reduction after the whole treatment course in the TCH arm, although it decreased at four cycles. In addition, the reduction in LVEF from baseline to the end of treatment was significant in the arm with anthracycline followed by trastuzumab (FEC-TCH), but not with TCH followed by anthracycline (TCH-FEC). A similar trend was observed in another study (21). Five-year follow-up results from the FinHER study on postoperative adjuvant chemotherapy reported that the reduction in LVEF was lower in the combined chemotherapy and trastuzumab arm than in the chemotherapy-alone arm (*P* = 0.006) (21). In the FinHER study, trastuzumab was used in combination with taxane or vinorelbine, followed by a regimen containing anthracycline. Thus, a trastuzumab-containing regimen was used before an anthracycline-containing regimen. The finding of the present study is in concordance with the FinHER study, suggesting that the order of trastuzumab with taxane followed by anthracycline may be better suited for cardiac safety than the reverse order of the sequence.

In this study, ILD was observed more frequently than in other studies. One reason might be that intensive review on CT was performed in all patients after one death according to IDMC request and that any minor change was all taken as positive, which might have resulted in more frequent findings on ILD in this study. In fact,

except for one patient who died in the FEC-TCH arm, no patients had grade 3 or worse ILD.

This study has some limitations. First, the randomization was discontinued due to one death from ILD, which made it impossible to compare among the three arms. Next and foremost was the small number of patients even in the TCH arm; thus, it is important to interpret the results with caution. Another limitation was the short follow-up time for survival analyses. This might have led to no improvement of survival in the pCR group compared to the non-pCR group. Longer follow-up is needed to validate the clinical utility of TCH for HER2-positive early breast cancer.

In conclusion, the pCR rate of the TCH arm was similar to previous reports of anthracycline-containing regimens. Survival in the TCH arm was good in patients with stage I or IIA HER2-positive breast cancer. Although ILD occurred during TCH treatment, no other new safety issues were reported. It was not possible to determine the preferable sequence of anthracycline and taxane because the statistical power was insufficient. However, the LVEF results suggested that TCH or TCH followed by FEC is preferable. TCH might be an option for early-stage HER2-positive breast cancer, although confirmatory studies are needed.

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## Conflict of interest statement

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