ORIGINAL ARTICLE

# Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

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## ABSTRACT

### BACKGROUND

Patients who have residual invasive carcinoma after the receipt of neoadjuvant chemotherapy for human epidermal growth factor receptor 2 (HER2)–negative breast cancer have poor prognoses. The benefit of adjuvant chemotherapy in these patients remains unclear.

### METHODS

We randomly assigned 910 patients with HER2-negative residual invasive breast cancer after neoadjuvant chemotherapy (containing anthracycline, taxane, or both) to receive standard postsurgical treatment either with capecitabine or without (control). The primary end point was disease-free survival. Secondary end points included overall survival.

### RESULTS

The result of the prespecified interim analysis met the primary end point, so this trial was terminated early. The final analysis showed that disease-free survival was longer in the capecitabine group than in the control group (74.1% vs. 67.6% of the patients were alive and free from recurrence or second cancer at 5 years; hazard ratio for recurrence, second cancer, or death, 0.70; 95% confidence interval [CI], 0.53 to 0.92; P=0.01). Overall survival was longer in the capecitabine group than in the control group (89.2% vs. 83.6% of the patients were alive at 5 years; hazard ratio for death, 0.59; 95% CI, 0.39 to 0.90; P=0.01). Among patients with triple-negative disease, the rate of disease-free survival was 69.8% in the capecitabine group versus 56.1% in the control group (hazard ratio for recurrence, second cancer, or death, 0.58; 95% CI, 0.39 to 0.87), and the overall survival rate was 78.8% versus 70.3% (hazard ratio for death, 0.52; 95% CI, 0.30 to 0.90). The hand–foot syndrome, the most common adverse reaction to capecitabine, occurred in 73.4% of the patients in the capecitabine group.

### CONCLUSIONS

After standard neoadjuvant chemotherapy containing anthracycline, taxane, or both, the addition of adjuvant capecitabine therapy was safe and effective in prolonging disease-free survival and overall survival among patients with HER2-negative breast cancer who had residual invasive disease on pathological testing. (Funded by the Advanced Clinical Research Organization and the Japan Breast Cancer Research Group; CREATE-X UMIN Clinical Trials Registry number, UMIN000000843.)

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A complete list of the investigators in the Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial is provided in the Supplementary Appendix, available at NEJM.org.

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Patients who have residual invasive breast cancer after the receipt of neoadjuvant chemotherapy have a high risk of relapse.[1] The rate of complete response as assessed on pathological testing (hereafter, pathological complete response) ranges from 13 to 22% among patients with human epidermal growth factor receptor 2 (HER2)–negative primary breast cancer.[1] Patients who do not have a pathological complete response after the receipt of neoadjuvant taxane and anthracycline chemotherapy have a 20 to 30% risk of relapse.[2] Patients with HER2-negative cancer who receive neoadjuvant chemotherapy often receive postoperative radiation therapy, whereas endocrine therapy is administered to patients with hormone-receptor–positive disease only.[3,4] No adjuvant chemotherapy has been established for patients who have residual invasive breast cancer after the receipt of neoadjuvant chemotherapy.

Capecitabine (Xeloda, Hoffmann–La Roche), an oral prodrug of fluorouracil, has been shown to be efficacious as adjuvant chemotherapy in patients with gastrointestinal cancer.[5-7] However, its efficacy in patients with breast cancer is unclear.[8,9] Capecitabine has been shown to be effective in patients with metastatic breast cancer[10-12] and is often used as second-line monotherapy in patients whose disease is resistant to anthracycline, taxane, or both.[3,13] We conducted the Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial, which was a multicenter, open-label, randomized, phase 3 trial that was designed to evaluate the efficacy and safety of adjuvant capecitabine monotherapy in patients with HER2-negative primary breast cancer who had residual invasive disease after the receipt of standard neoadjuvant chemotherapy containing anthracycline, taxane, or both.

## Methods

### Patients

The trial protocol (including the statistical analysis plan) is available with the full text of this article at NEJM.org. We recruited patients who had HER2-negative breast cancer of stage I through IIIB and pathologically assessed residual cancer cells (no pathological complete response) after neoadjuvant chemotherapy with anthracycline, taxane, or both (Fig. 1). Patients who had residual components of ductal carcinoma in situ were assessed as having a pathological complete response on the basis of the National Surgical Adjuvant Breast and Bowel Project criteria.[14] Patients with tumor-positive lymph nodes[15] were also eligible. Central pathological review independently confirmed the presence of residual invasive cancer cells. The pathological effect of neoadjuvant chemotherapy was graded from 0 to 3 according to the response criteria of the Japanese Breast Cancer Society.[16] Grade 0 indicates no response (almost no change in cancer cells after treatment), grade 1a a mild response (mild changes in cancer cell, regardless of the area, or marked changes in cancer cell seen in less than one third of cancer cells), grade 1b a moderate response (marked changes in one third or more but less than two thirds of tumor cells), grade 2 a marked response (marked changes in two thirds or more of tumor cells), and grade 3 a complete response (necrosis or disappearance of all tumor cells, replacement of all cancer cells by granuloma-like or fibrous tissue, and, in the case of complete disappearance of cancer cells, pretreatment pathological evidence of the presence of cancer).

Other key eligibility criteria were an age of 20 to 74 years, HER2-negative status (score of 0 or 1 on an immunohistochemical test [range, 0 to 3, with a score of 0 or 1 indicating HER2-negative breast cancer, a score of 2 a marginal result, and a score of 3 HER2-positive breast cancer; in the case of a marginal result, HER2 status was examined by means of fluorescence in situ hybridization to establish a positive or negative result] or a negative result on fluorescence in situ hybridization), and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability). Key exclusion criteria were the presence of breast cancer in both breasts, other malignant conditions or synchronic multiple cancers, and previous treatment with oral fluorouracil.

Eligible patients were centrally enrolled after pathological assessment and were randomly assigned in a 1:1 ratio to receive either capecitabine plus standard therapy or standard therapy alone (control). Randomization was performed at the data center with the use of concealed assignments and with the use of a minimization method with the following balancing adjustment factors: estrogen-receptor status (positive vs. negative), age (≤50 years vs. >50 years), taxane use

(yes vs. no vs. ≥4 cycles of docetaxel and cyclophosphamide), axillary lymph-node metastasis on histologic assessment (no nodes vs. 1, 2, or 3 nodes vs. ≥4 nodes vs. unknown number), fluorouracil use (yes vs. no), and participating institution.

### TRIAL DESIGN AND OVERSIGHT

The trial treatments were standard postsurgical treatments,[3,4] which included endocrine therapy in patients with estrogen-receptor–positive disease and radiotherapy (if indicated), with or without capecitabine. Endocrine therapy was administered as follows: 5 years of tamoxifen or toremifene, combined with a gonadotropin-releasing hormone analogue as needed, in premenopausal patients or 5 years of aromatase inhibitors, tamoxifen, or toremifene in postmenopausal patients. After surgery, the capecitabine group received oral capecitabine (at a dose of 1250 mg per square meter of body-surface area, twice per day, on days 1 to 14) every 3 weeks for six or eight cycles. The concomitant administration of postsurgical endocrine therapy was allowed. Postsurgical radiotherapy could be given before or after randomization and could be concomitant with postsurgical endocrine therapy. Other anticancer drugs were not allowed until recurrence. Follow-up was scheduled through the end of the trial. Patients visited the trial institutions every 6 months and underwent mammographic screening once per year to assess breast-cancer recurrence.

The trial was designed by the lead authors and monitored by an independent data and safety monitoring committee. All the patients provided written informed consent. The trial was approved by the institutional review board at each institution and conducted in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies of the respective ministries of Japan and South Korea. Data were collected and centrally monitored at the Comprehensive Support Project for Oncology Research. To ensure data quality, some trial institutions were chosen by random sampling for auditing.

All the authors vouch for the accuracy and completeness of the data and analyses and for the adherence of the trial to the protocol. The first draft of the manuscript was prepared by the first and last authors with assistance from a professional medical writer, funded by the Japan Breast Cancer Research Group. All the authors made the decision to submit the manuscript for publication. The trial was funded by the Advanced Clinical Research Organization and the Japan Breast Cancer Research Group, and the

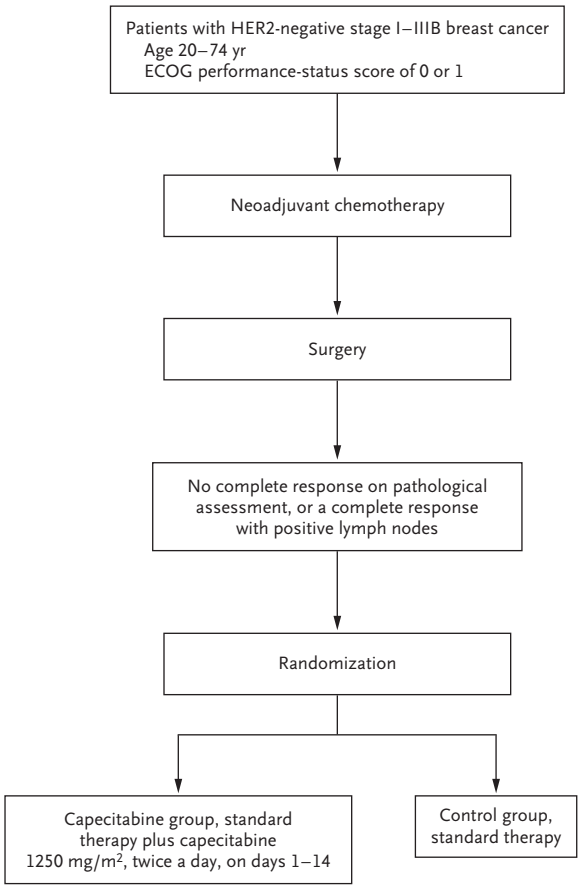


**Figure 1. Trial Design.**

Neoadjuvant chemotherapy involved at least four cycles of an anthracycline. However, if the anthracycline was administered for less than four cycles, one of the following four regimens could be used: fluorouracil and epirubicin (at a dose of ≥100 mg per square meter of body-surface area) and cyclophosphamide (FEC) for three cycles, followed by docetaxel at a dose of 75 mg per square meter for three cycles; FEC for three cycles, followed by docetaxel at a dose of 75 mg per square meter and cyclophosphamide at a dose of 600 mg per square meter (TC) for three cycles; TC for three cycles, followed by FEC for three cycles; or TC only for four cycles. Patients who had serious adverse events or disease progression were included if they completed at least two cycles of chemotherapy. If patients had positive lymph nodes, combined chemotherapy with an anthracycline and taxane (docetaxel or paclitaxel, as chosen by the physician) was recommended. The Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale of 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability related to tumor. Standard therapy included 5 years of endocrine therapy for hormone-receptor–positive cancer, no further systemic treatment for hormone-receptor–negative cancer, and radiotherapy if indicated. HER2 denotes human epidermal growth factor receptor 2.

sponsors of the trial were the Japan Breast Cancer Research Group, the Korean Breast Cancer Society, and the Korean Cancer Study Group. The funders and sponsors had no role in the trial design, data collection and analysis, or the interpretation of the results. In South Korea, capecitabine was provided free of charge by Roche Korea, which had no other role in the trial. In Japan, supply of capecitabine by a pharmaceutical company for use in a clinical trial is not permitted by law, and capecitabine was administered to patients in accordance with health insurance provisions (national or public health insurance covered ≥70% of the cost, and the remainder was paid by private health insurance or others).

### END POINTS

The primary end point of the trial was disease-free survival, which was defined as the time from randomization to recurrence, the development of a second cancer, or death from any cause. Secondary end points included overall survival, which was defined as the time from randomization to death from any cause. Data for patients who did not have an event of interest were censored at the date of the last follow-up. For the safety evaluation, adverse events that occurred within 6 months after randomization were assessed and reported according to a list of known adverse reactions to capecitabine and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[17] Events of the hand–foot syndrome were graded from 1 to 3, with higher grades indicating more severe symptoms or disability (see the Supplementary Appendix, available at NEJM.org).[10]

### STATISTICAL ANALYSIS

Survival curves were estimated with the use of the Kaplan–Meier method, and hazard ratios with 95% confidence intervals were determined with the use of a Cox proportional-hazards model. On the basis of the Cox model, prespecified subgroup analyses for important background or prognostic factors were conducted. Additional post hoc subgroup analyses of body-mass index (the weight in kilograms divided by the square of the height in meters) in all patients and of body-mass index in patients with hormone-receptor–negative disease were conducted. For the safety analysis, the numbers and percentages of patients with adverse events of each grade were calculated.

The primary efficacy analysis was performed on the full analysis set according to the intention-to-treat principle. The full analysis set included all the patients who had undergone randomization except those who did not meet any of the major eligibility criteria (e.g., because of errors in assignment of clinical stage of cancer before neoadjuvant chemotherapy) and those without any follow-up data after randomization. Sensitivity analyses were performed in the per-protocol population, which included patients from the full analysis set who received the trial treatment per the protocol and fulfilled all minor eligibility criteria (e.g., with regard to range of laboratory examinations at registration). The safety population included all the patients who started the trial treatment.

The hazard ratio for recurrence, second cancer, or death in the analysis of disease-free survival in the capecitabine group was assumed to be 0.74.[14,18-21] With the recruitment period set at 5 years, the follow-up period at a maximum of 5 years, the beta level at 0.2, and the alpha level at 0.05 (two-sided), we calculated that the trial would need to include 427 patients in each group.[22] Thus, we planned to enroll 900 patients (450 patients per group). Interim safety analyses were prespecified in order to investigate the dose of capecitabine and number of cycles that could be received with an acceptable safety profile. An interim efficacy analysis of disease-free survival with the use of the Lan–DeMets alpha-spending function method (O'Brien–Fleming type)[23] was prespecified to occur at 2 years after the enrollment of patients was complete. A one-sided P value (at a significance level of 0.025) was used for decision making in all the analyses, and two-sided P values (at a significance level of 0.05) are provided in this article, according to usual practice.

## RESULTS

### PATIENTS

From February 2007 through July 2012, a total of 910 patients (606 patients from 62 institutions in Japan and 304 patients from 22 institutions in South Korea) were enrolled (see the Supplementary Appendix). Patients were randomly assigned

equally to the capecitabine group and the control group (455 patients in each group). This trial was registered late owing to an administrative error, and the registration information was disclosed on November 1, 2007. At the time of registration, 19 patients had been enrolled.

After the exclusion of patients for ineligibility (16 patients), withdrawal of informed consent (3), violation of informed consent (2), and lack of follow-up data (2), a total of 887 patients were included in the full analysis set (443 patients in the capecitabine group and 444 in the control group). One patient in the capecitabine group did not receive the assigned capecitabine but received control therapy instead, and 1 patient assigned to the control group received capecitabine instead. These patients were included in the originally assigned groups in the intention-to-treat analysis of efficacy. In the safety analysis, however, these patients were included in the group according to the actual regimen received. A total of 844 patients (415 patients in the capecitabine group and 429 in the control group) were included in the per-protocol set. Details are provided in Figure S1 in the Supplementary Appendix.

The characteristics of the patients at baseline were similar in the two groups (Table 1). The median age of the patients was 48 years (range, 25 to 74). Approximately 40% of the patients had stage IIIA or IIIB breast cancer, and 32.2% had triple-negative breast cancer (i.e., negative for estrogen receptors, progesterone receptors, and HER2). A total of 95.3% of the patients had received an anthracycline and taxane as neoadjuvant chemotherapy (82.2% of the patients had received sequential therapy and 13.1% had received concurrent therapy).

On the basis of the interim safety analysis involving the first 50 patients who were treated with six cycles of capecitabine, the independent data and safety monitoring committee recommended in January 2010 that the capecitabine treatment be extended to eight cycles (24 weeks). Consequently, 159 patients were treated with six cycles of capecitabine and 283 with eight cycles, of whom 57.9% and 37.8%, respectively, completed capecitabine treatment with the planned dose, 23.9% and 36.7% completed capecitabine treatment with dose reduction, and 18.2% and 25.4% discontinued capecitabine treatment. The mean relative dose intensity was 87.9% in patients who received six cycles and 78.7% in those who received eight cycles.

### DISEASE-FREE SURVIVAL AND OVERALL SURVIVAL

The prespecified interim efficacy analysis that was conducted on March 11, 2015, showed that the primary end point was met, so the independent data and safety monitoring committee recommended early termination of the trial as specified in the protocol. Therefore, this trial was terminated early, and data up to the data-cutoff date of September 30, 2015, were fixed on June 16, 2016, and were included in the final analysis performed on July 28, 2016. The median follow-up was 3.6 years.

The rate of disease-free survival was higher in the capecitabine group than in the control group (82.8% vs. 73.9% of the patients were alive and free from recurrence or second cancer at 3 years, and 74.1% vs. 67.6% were alive and free from recurrence or second cancer at 5 years), and the time to recurrence, second cancer, or death was longer in the capecitabine group than in the control group (hazard ratio for recurrence, second cancer, or death, 0.70; 95% confidence interval [CI], 0.53 to 0.92; P=0.01) (Fig. 2A). The overall survival rate was higher in the capecitabine group than in the control group (94.0% vs. 88.9% of the patients were alive at 3 years, and 89.2% vs. 83.6% were alive at 5 years), and survival was longer in the capecitabine group than in the control group (hazard ratio for death, 0.59; 95% CI, 0.39 to 0.90; P=0.01). The median survival for any end point was not reached in either group (Fig. 2B).

The results of the sensitivity analyses regarding disease-free survival and overall survival in the per-protocol population were similar to those in the full analysis set (Fig. S2 in the Supplementary Appendix). The benefits of capecitabine with regard to disease-free survival and overall survival were consistent across the prespecified subgroups (Fig. 3, and Fig. S3 in the Supplementary Appendix). Among patients with hormone-receptor–negative (triple-negative) disease, the rate of disease-free survival was 69.8% in the capecitabine group, as compared with 56.1% in the control group (hazard ratio for recurrence, second cancer, or death, 0.58; 95% CI, 0.39 to 0.87), and the overall survival rate was 78.8% versus

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Capecitabine Group (N=443) | Control Group (N=444) |
|---|---|---|
| Age at enrollment — yr | | |
| Median | 48 | 48 |
| Range | 25–74 | 25–74 |
| Menopausal status — no. (%) | | |
| Premenopausal | 262 (59.1) | 248 (55.9) |
| Postmenopausal | 181 (40.9) | 196 (44.1) |
| Body-mass index† | | |
| Median | 22.6 | 23.0 |
| Range | 15.6–39.9 | 15.6–41.2 |
| Tumor size at diagnosis — no./total no. (%) | | |
| ≤2 cm | 68/442 (15.4) | 61/444 (13.7) |
| >2 to ≤5 cm | 244/442 (55.2) | 275/444 (61.9) |
| >5 cm | 65/442 (14.7) | 69/444 (15.5) |
| Skin or chest-wall infiltration of any size — no./total no. (%) | 65/442 (14.7) | 39/444 (8.8) |
| Hormone-receptor status — no. (%) | | |
| Estrogen-receptor positive or progesterone-receptor positive | 304 (68.6) | 297 (66.9) |
| Estrogen-receptor negative and progesterone-receptor negative | 139 (31.4) | 147 (33.1) |
| Neoadjuvant chemotherapy — no. (%) | | |
| Sequential anthracycline and taxane | 357 (80.6) | 372 (83.8) |
| Concurrent anthracycline and taxane | 63 (14.2) | 53 (11.9) |
| Anthracycline-containing chemotherapy only or docetaxel and cyclophosphamide only | 23 (5.2) | 19 (4.3) |
| Fluorouracil plus anthracycline‡ | 262 (59.1) | 271 (61.0) |
| Pathological-effect grade — no./total no. (%)§ | | |
| 0 | 19/434 (4.4) | 13/435 (3.0) |
| 1a or 1b | 232/434 (53.5) | 220/435 (50.6) |
| 2 or 3 | 183/434 (42.2) | 202/435 (46.4) |
| No. of lymph nodes involved on histologic assessment — no. (%) | | |
| 0 | 176 (39.7) | 171 (38.5) |
| 1–3 | 165 (37.2) | 174 (39.2) |
| ≥4 | 102 (23.0) | 99 (22.3) |
| Adjuvant endocrine therapy — no. (%) | | |
| Yes | 298 (67.3) | 304 (68.5) |
| No | 145 (32.7) | 140 (31.5) |
| Radiotherapy — no. (%)¶ | | |
| Yes | 321 (72.5) | 326 (73.4) |
| No | 122 (27.5) | 118 (26.6) |

* There were no significant differences between the two groups. The following adjustment factors were used to balance randomization with the use of a minimization method: estrogen-receptor status (positive vs. negative), age (≤50 years vs. >50 years), taxane use (yes vs. no vs. ≥4 cycles of docetaxel and cyclophosphamide), axillary lymph-node metastasis on histologic assessment (no nodes vs. 1, 2, or 3 nodes vs. ≥4 nodes vs. unknown number), fluorouracil use (yes vs. no), and participating institution.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Fluorouracil was administered intravenously as a bolus dose.

§ The pathological effect of neoadjuvant chemotherapy was graded from 0 to 3 according to the response criteria of the Japanese Breast Cancer Society.[16] Grade 0 indicates no response (almost no change in cancer cells after treatment), grade 1 slight response, grade 1a a mild response (mild changes in cancer cells regardless of the area, or marked changes in cancer cell seen in less than one third of cancer cells), grade 1b a moderate response (marked changes in one third or more but less than two thirds of tumor cells), grade 2 a marked response (marked changes in two thirds or more of tumor cells), and grade 3 a complete response (necrosis or disappearance of all tumor cells, replacement of all cancer cells by granuloma-like or fibrous tissue, and, in the case of complete disappearance of cancer cells, pretreatment pathological evidence of the presence of cancer).

¶ Radiotherapy was for the following regions: conserving breast only, conserving breast and regional lymph nodes, chest wall or regional lymph nodes, and unknown region.

70.3% (hazard ratio for death, 0.52; 95% CI, 0.30 to 0.90) (Fig. 2C and 2D). Among patients with hormone-receptor–positive disease, the rate of disease-free survival was 76.4% in the capecitabine group, as compared with 73.4% in the control group (hazard ratio for recurrence, second cancer, or death, 0.81; 95% CI, 0.55 to 1.17), and the overall survival rate was 93.4% versus 90.0% (hazard ratio for death, 0.73; 95% CI, 0.38 to 1.40) (Fig. S4A and S4B in the Supplementary Appendix). Post hoc subgroup analyses of disease-free survival and overall survival showed no significant interaction between the subgroup of patients with a high body-mass index (≥25.0) and the subgroup of those with a low body-mass index (<25.0) (Fig. 3, and Fig. S3 in the Supplementary Appendix).

### SAFETY

All the patients who started the trial treatment were included in the safety analysis (443 patients in the capecitabine group and 459 in the control group) (Table 2). In the capecitabine group, the hand–foot syndrome was the most frequent adverse event, occurring in 325 patients (73.4%), including 49 patients (11.1%) with a grade 3 event. The common hematologic adverse events (occurring in >40% of patients) in the capecitabine group were leukopenia, thrombocytopenia, neutropenia, and anemia. The common nonhematologic adverse events (occurring in >20% of patients) in the capecitabine group were fatigue, nausea, diarrhea, stomatitis, and increases in the alanine aminotransferase, bilirubin, lactate dehydrogenase, aspartate aminotransferase, and alkaline phosphatase levels. Most adverse events were grade 1 or 2 in severity. In the capecitabine group, neutropenia of grade 3 or 4 was noted in 6.3% of the patients, diarrhea of grade 3 or 4 in 2.9%, and leukopenia of grade 3 or 4 in 1.6%. Serious adverse events that were considered by the investigators to be related to capecitabine occurred in 4 patients, including neutropenia and diarrhea in 1 patient and epigastric pain, abdominal pain, and diarrhea in 1 patient each. All the serious adverse events resolved and were nonfatal.

## DISCUSSION

This trial showed that capecitabine that was administered as a postoperative adjuvant therapy after neoadjuvant chemotherapy in patients with residual invasive tumors or lymph-node metastasis prolonged disease-free survival and overall survival. Two aspects of this trial may account for the positive result. First, the trial targeted a population of patients who did not have a pathological complete response, a group whose survival outcomes are known to be unfavorable. Among patients who did not have a pathological complete response, more than 20% have a relapse within 5 years,[2] and approximately half the patients with triple-negative disease have recurrence.[1] We excluded patients who had a pathological complete response, who were likely to be cured with standard chemotherapy regimens. Therefore, this exclusion enriched the trial population for patients who may benefit from additional therapy.

Second, this trial used an effective schedule of the fluorouracil-based antimetabolite; capecitabine therapy was compared with no chemotherapy as postoperative adjuvant therapy. In fact, 60% of the patients in our trial had residual invasive cancer after receiving an intravenous bolus infusion of fluorouracil as a component of neoadjuvant chemotherapy. Furthermore, a working hypothesis was formed regarding the mechanism of drug-combination effect. Anthracyclines and taxanes are able to induce thymidine phosphorylase, an enzyme that activates capecitabine.[24] Chemotherapeutic agents may have schedule dependency.[25-28] In particular, fluorouracil has been shown to be schedule-dependent. Fluorouracil is a phase-specific antimetabolite with a short half-life, and infusional schedules and oral drugs have been developed to enhance its efficacy.[29]

However, several trials of adjuvant capecitabine that was administered in combination with chemotherapy did not show an advantage over regimens without capecitabine.[8,9,30-32] In the GEICAM/2003-10 trial conducted by Grupo Español de Investigacíon en Cáncer de Mama (Spanish Breast Cancer Group), invasive disease–free survival was significantly longer among patients with node-positive early breast cancer who received adjuvant epirubicin and cyclophosphamide followed by docetaxel than among those who received adjuvant epirubicin and docetaxel followed by capecitabine.[8] In the Finland Capecitabine Trial (FinXX), the integration of capecitabine into adjuvant docetaxel therapy followed by cyclophosphamide and epirubicin did not prolong recurrence-free survival, as compared with adjuvant docetaxel followed by cyclophosphamide, epirubicin, and

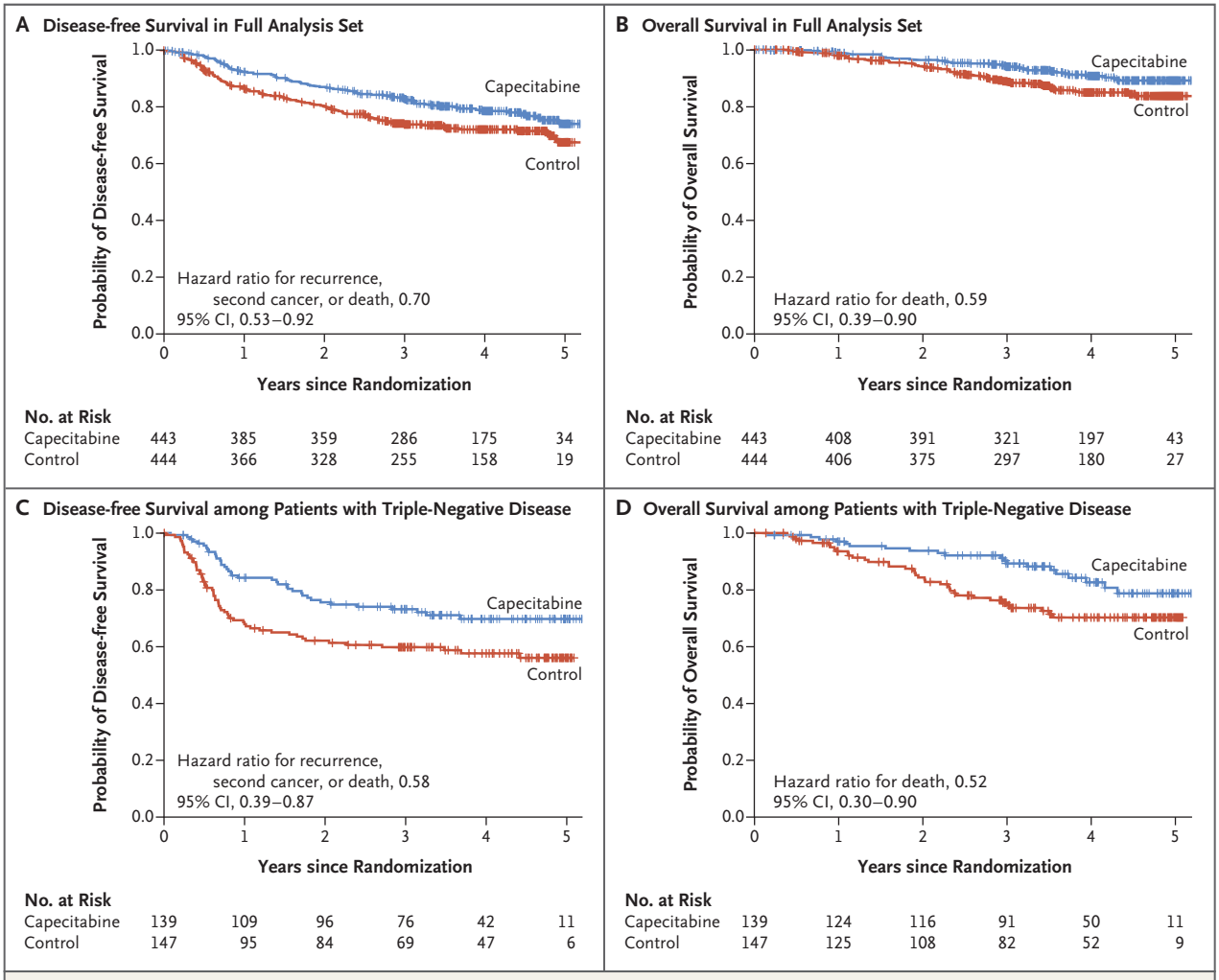


**Figure 2. Kaplan–Meier Estimates of Disease-free Survival and Overall Survival.**

Panels A and B show disease-free survival and overall survival, respectively, in the full analysis set (primary analysis). Tick marks indicate censored data. Panels C and D show disease-free survival and overall survival, respectively, in the subgroup of patients with triple-negative breast cancer (i.e., breast cancer that was negative for estrogen receptors, progesterone receptors, and HER2).

fluorouracil.[9] Furthermore, although the primary end point of disease-free survival was not met in a phase 3 adjuvant trial[33] comparing doxorubicin plus cyclophosphamide followed by docetaxel plus capecitabine with doxorubicin plus cyclophosphamide followed by docetaxel alone, a significant prolongation in overall survival, a secondary end point, was seen with the combination of docetaxel plus capecitabine. The majority of the patients included in the trial had a low risk of recurrence, as identified by estrogen-receptor–positive status and low Ki67 status.[33]

Moreover, the percentages of patients with triple-negative disease also differed in the two trials.[8,9] In the GEICAM/2003-10 trial, 12% of the patients had triple-negative disease, and no superiority of a capecitabine-containing adjuvant regimen was shown, as compared with control (hazard ratio for death or recurrence with invasive disease, 1.19; 95% CI, 0.70 to 2.04).[8] In

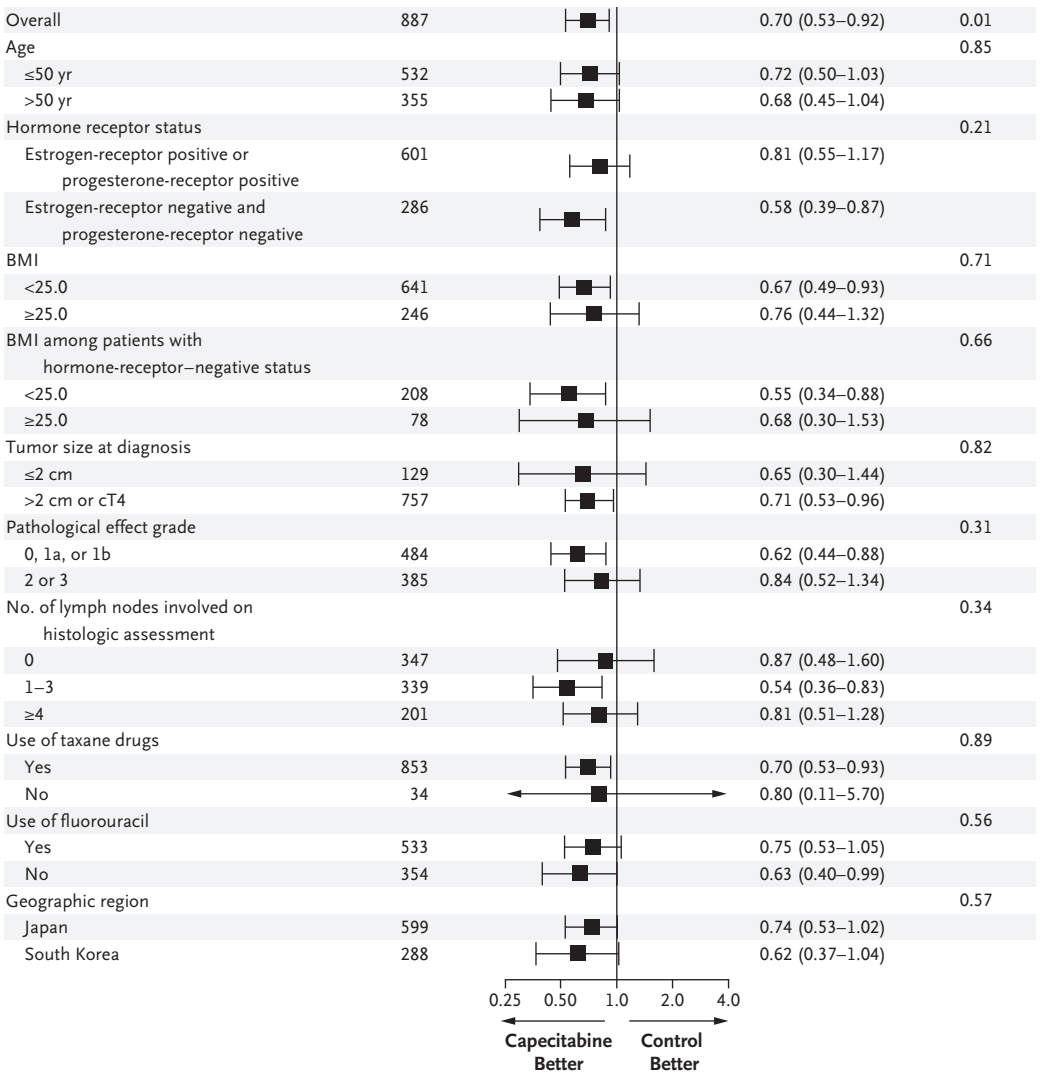


**Figure 3. Subgroup Analysis of Disease-free Survival in the Full Analysis Set.**

On the basis of the Cox model, prespecified subgroup analyses for background or prognostic factors were conducted to estimate hazard ratios with 95% confidence intervals and to test for interaction among subgroups with the use of two-sided P values. Post hoc subgroup analyses were conducted regarding body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) in all patients and BMI in patients with hormone-receptor–negative disease. A tumor size of cT4 indicates a tumor of any size with direct extension to the chest wall or skin. Data on tumor size were missing for one patient in the capecitabine group. The pathological effect of neoadjuvant chemotherapy was graded from 0 to 3 according to the response criteria of the Japanese Breast Cancer Society[16]: grade 0 indicates no response, grade 1a a mild response, grade 1b a moderate response, grade 2 a marked response, and grade 3 a complete response. Data on pathological effect were missing for nine patients in each group. Arrows indicate that the limits of the confidence interval are not shown.

**Table 2. Adverse Events Assessed within 6 Months after Randomization.**

| Event | Capecitabine Group (N=443) | | | | | Control Group (N=459) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 3 or 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 3 or 4 |
| | *no. of patients* | | | | % | *no. of patients* | | | | % |
| Hematologic adverse event | | | | | | | | | | |
| Neutropenia | 84 | 81 | 26 | 2 | 6.3 | 28 | 15 | 0 | 0 | — |
| Leukopenia | 130 | 143 | 6 | 1 | 1.6 | 67 | 19 | 1 | 0 | 0.2 |
| Thrombocytopenia | 203 | 37 | 3 | 0 | 0.7 | 32 | 2 | 0 | 0 | — |
| Anemia | 165 | 10 | 0 | 0 | — | 46 | 7 | 0 | 0 | — |
| Nonhematologic adverse event | | | | | | | | | | |
| Diarrhea | 67 | 17 | 11 | 2 | 2.9 | 1 | 0 | 0 | 0 | — |
| Fatigue | 88 | 20 | 5 | 0 | 1.1 | 8 | 1 | 0 | 0 | — |
| Anorexia | 61 | 12 | 3 | 0 | 0.7 | 5 | 1 | 1 | 0 | 0.2 |
| Bilirubin level increased | 99 | 41 | 2 | 0 | 0.5 | 6 | 2 | 0 | 1 | 0.2 |
| Aspartate aminotransferase level increased | 120 | 6 | 1 | 0 | 0.2 | 27 | 1 | 2 | 0 | 0.4 |
| Mucositis or stomatitis | 80 | 13 | 1 | 0 | 0.2 | 2 | 0 | 0 | 0 | — |
| Vomiting | 25 | 6 | 1 | 0 | 0.2 | 2 | 0 | 1 | 0 | 0.2 |
| Nausea | 92 | 6 | 0 | 0 | — | 1 | 2 | 0 | 0 | — |
| Alanine aminotransferase level increased | 143 | 15 | 0 | 0 | — | 37 | 4 | 2 | 0 | 0.4 |
| Alkaline phosphatase level increased | 110 | 3 | 0 | 0 | — | 65 | 2 | 1 | 0 | 0.2 |
| Lactate dehydrogenase level increased | 141 | — | — | — | — | 36 | — | — | — | — |
| Creatinine level increased | 22 | 2 | 0 | 0 | — | 12 | 2 | 0 | 0 | — |
| Hand–foot syndrome* | 165 | 111 | 49 | — | 11.1 | — | — | — | — | — |

* The hand–foot syndrome was graded from 1 to 3 with the use of the following criteria[10]: grade 1 was defined as numbness, dermal hypersensitivity, tingling sensation, painless swelling, or painless erythema (symptomatic criteria), with no restriction on activities of daily living (functional criteria); grade 2 as swelling with painful erythema (symptomatic criteria), with restrictions on activities of daily living (functional criteria); and grade 3 as wet desquamation, ulcers, edema, or severe pain (symptomatic criteria), with activities of daily living prevented (functional criteria). The percent of patients with any grade of this event was 73.4%.

FinXX, 13% of the patients had triple-negative cancer, and recurrence-free survival was longer with the capecitabine-containing regimen than with control (hazard ratio for recurrence or death, 0.48; 95% CI, 0.26 to 0.88).[9] In our trial, 30% of the patients had triple-negative disease. The prolongation with capecitabine versus control in disease-free survival (hazard ratio for recurrence, second cancer, or death, 0.58) and overall survival (hazard ratio for death, 0.52) was particularly notable among patients with triple-negative disease. Among patients with hormone-receptor–positive disease, we observed a similar tendency with a reduced magnitude (hazard ratio for recurrence, second cancer, or death, 0.81; hazard ratio for death, 0.73). A randomized trial by Coalición Iberoamericana de Investigación en Oncología Mamaria (CIBOMA/2004-01/GEICAM/2003-11; ClinicalTrials.gov number, NCT00130533), which has a design similar to that used in our trial, is currently in progress to evaluate the efficacy of adjuvant capecitabine after standard chemotherapy in patients with triple-negative cancer.[34]

With respect to safety, the known adverse reactions of capecitabine occurred frequently in our trial, although most reactions were not severe. The hand–foot syndrome — the most common adverse reaction of capecitabine — occurred in nearly 75% of the patients who received capecitabine. Other common events were myelotoxic effects, hepatic dysfunction, and gastrointestinal symptoms. The doses of capecitabine that were used in our trial were within the range that has been approved in Western countries. In accordance with international standards,[35] the following dosing regimen was used for capecitabine: 1250 mg per square meter, twice per day, on days 1 to 14 every 3 weeks, followed by 1-week withdrawal. Although some patients had a dose reduction or withdrawal of capecitabine because of adverse events (mainly the hand–foot syndrome), the relative dose intensity in approximately 80% of the patients was maintained during the treatment period of six or eight cycles. For gastrointestinal cancer, the gastrointestinal toxicity of fluoropyrimidines (including capecitabine) has been reported to be lower in Asian patients than in white patients.[36,37] In addition, the pharmacokinetic profile of capecitabine may differ slightly between Asians and non-Asians; therefore, racial differences in the safety profile of capecitabine after standard anthracycline or taxane chemotherapy need to be carefully considered in patients with breast cancer. With a suitable modification of dose or schedule to manage the toxic effects of capecitabine, the results of our trial are expected to be applicable to patients in Western countries.

In conclusion, capecitabine showed effectiveness as an adjuvant option in patients with HER2-negative breast cancer who had residual invasive disease after standard neoadjuvant chemotherapy. Our trial showed that adjuvant capecitabine therapy prolonged disease-free survival and overall survival among patients with breast cancer who had a poor prognosis, including those with triple-negative disease, and was associated with expected toxic effects.

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## APPENDIX

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