

Phase III Trial of Adjuvant Capecitabine After Standard Neo-/Adjuvant Chemotherapy in Patients With Early Triple-Negative Breast Cancer (GEICAM/2003-11_CIBOMA/2004-01)

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abstract

PURPOSE Operable triple-negative breast cancers (TNBCs) have a higher risk of relapse than non-TNBCs with standard therapy. The GEICAM/2003-11_CIBOMA/2004-01 trial explored extended adjuvant capecitabine after completion of standard chemotherapy in patients with early TNBC.

PATIENTS AND METHODS Eligible patients were those with operable, node-positive—or node negative with tumor 1 cm or greater—TNBC, with prior anthracycline- and/or taxane-containing chemotherapy. After central confirmation of TNBC status by immunohistochemistry, patients were randomly assigned to either capecitabine or observation. Stratification factors included institution, prior taxane-based therapy, involved axillary lymph nodes, and centrally determined phenotype (basal v nonbasal, according to cytokeratins 5/6 and/or epidermal growth factor receptor positivity by immunohistochemistry). The primary objective was to compare disease-free survival (DFS) between both arms.

RESULTS Eight hundred seventy-six patients were randomly assigned to capecitabine ($n = 448$) or observation ($n = 428$). Median age was 49 years, 55.9% were lymph node negative, 73.9% had a basal phenotype, and 67.5% received previous anthracyclines plus taxanes. Median length of follow-up was 7.3 years. DFS was not significantly prolonged with capecitabine versus observation [hazard ratio (HR), 0.82; 95% CI, 0.63 to 1.06; $P = .136$]. In a preplanned subgroup analysis, nonbasal patients seemed to derive benefit from the addition of capecitabine with a DFS HR of 0.53 versus 0.94 in those with basal phenotype (interaction test $P = .0694$) and an HR for overall survival of 0.42 versus 1.23 in basal phenotype (interaction test $P = .0052$). Tolerance of capecitabine was as expected, with 75.2% of patients completing the planned 8 cycles.

CONCLUSION This study failed to show a statistically significant increase in DFS by adding extended capecitabine to standard chemotherapy in patients with early TNBC. In a preplanned subset analysis, patients with nonbasal phenotype seemed to obtain benefit with capecitabine, although this will require additional validation.

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INTRODUCTION

Early triple-negative breast cancer (TNBC) can be cured with local-regional therapy plus adjuvant chemotherapy, usually anthracycline- and/or taxane-based combinations. However, despite these therapies, a proportion of patients eventually experience relapse and die. A recent analysis of data from the

National Cancer Institute SEER reported a 3-year relapse rate of approximately 8%, 15%, and 40% for patients with stages I, II, and III TNBC,¹ respectively; therefore, new adjuvant options are necessary to improve the prognosis of this breast cancer subtype.

Capecitabine is an oral prodrug of fluorouracil approved for the treatment of metastatic breast cancer in

ASSOCIATED CONTENT

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Data Supplement

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patients with prior progression after anthracyclines and taxanes and is therefore partially non-cross resistant with these two classes of agents.² On the basis of this concept, we carried out a trial in which capecitabine was sequentially added to standard (neo)adjuvant chemotherapy in operable TNBC to explore the ability of the drug to reduce the rate of relapse and increase the survival of this disease.

PATIENTS AND METHODS

The GEICAM/2003-11_CIBOMA/2004-01 trial is an open-label, randomized phase III study that was conducted in compliance with the International Council for Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The study was reviewed and approved by the independent ethics committees or institutional review boards of all participating institutions. Written informed

consent was obtained from all patients before any study-related procedures were performed.

Patient Eligibility

Eligible patients included women with hormone receptor-negative (immunohistochemistry staining of estrogen and progesterone receptors < 1%) and human epidermal growth factor 2-negative operable breast cancer, with invasive adenocarcinoma histologically confirmed. Patients had received 6 to 8 cycles of standard anthracycline- and/or taxane-containing chemotherapy in the (neo)adjuvant setting, followed by radiation therapy according to institutional guidelines. In the case of node-negative disease, 4 cycles of doxorubicin and cyclophosphamide were allowed. Eligible patients were those with ipsilateral axillary node involvement classified as pN1a, pN2a, or pN3a—excluding metastatic infraclavicular lymph

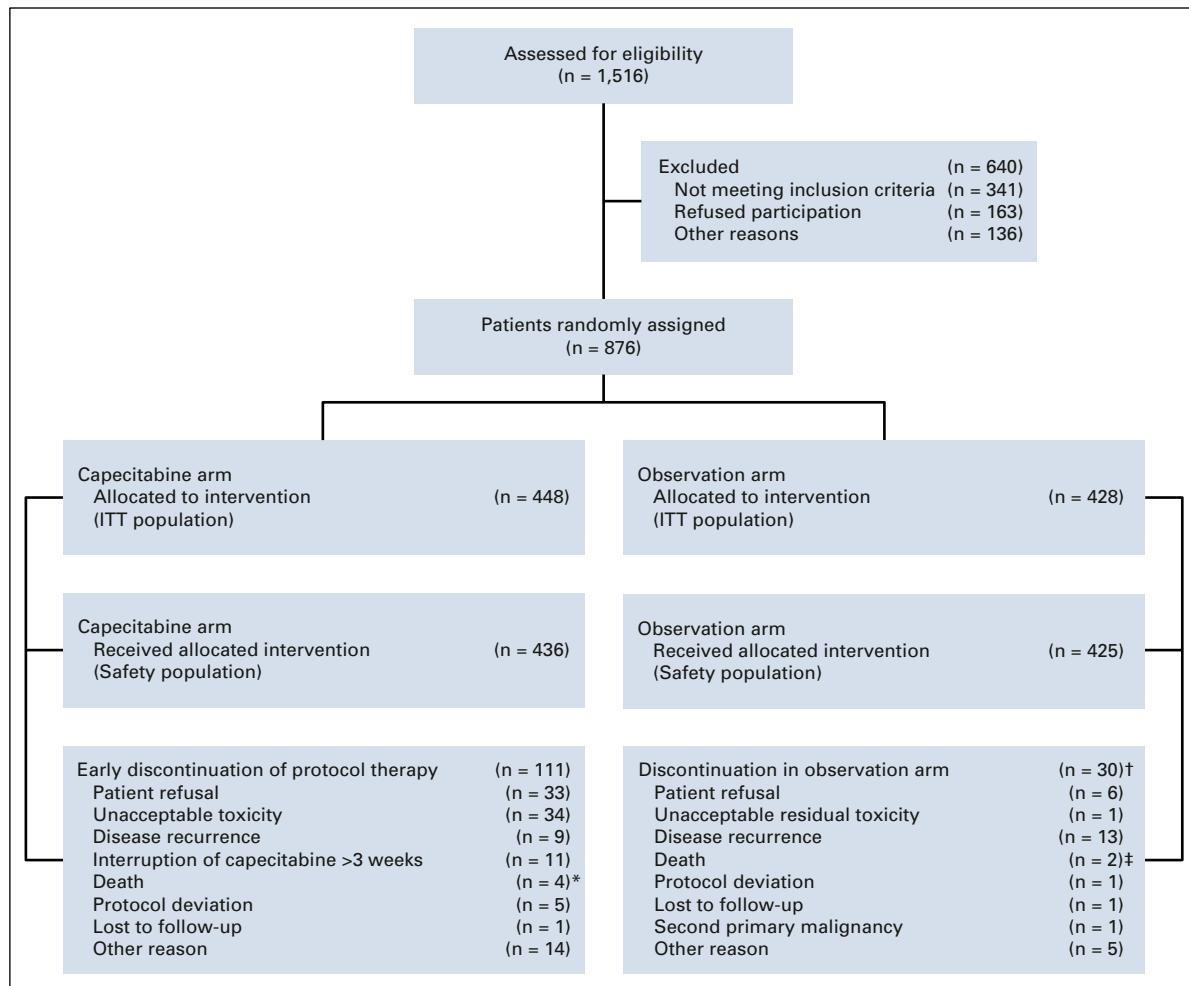


FIG 1. All patients enrolled (N = 876) were included in the efficacy analyses. All patients who had received at least 1 cycle of study treatment (n = 861) were evaluated for safety. Safety population: In the capecitabine arm, all patients who have completed at least one cycle of study treatment and in the observation arm, all patients with a follow-up period \geq 14 days. *Reasons of death on these patients: psychiatric disorder, cerebral hemorrhage, septic shock secondary to respiratory infection and stroke (not related with capecitabine). †Discontinuation of initial follow-up period (equivalent to treatment period in capecitabine arm). ‡Reasons of death on these patients: acute myocardial infarction and pulmonary sepsis.

TABLE 1. Patients' Demographics and Baseline Disease Characteristics According to Study Arm (intention-to-treat population)

| Demographic or Characteristic | Capecitabine Arm (n = 448), No. (%) | Observation Arm (n = 428), No. (%) |
|--------------------------------|--|---------------------------------------|
| Median age, years (range) | 50.0 (20.0-79.0) | 49.0 (23.0-82.0) |
| Region | | |
| Spain | 272.0 (60.7) | 260.0 (60.7) |
| Latin America | 176.0 (39.3) | 168.0 (39.3) |
| Race | | |
| White | 313.0 (69.9) | 309.0 (72.2) |
| Hispanic | 107.0 (23.9) | 97.0 (22.7) |
| African American | 16.0 (3.6) | 11.0 (2.6) |
| Other | 12.0 (2.7) | 11.0 (2.6) |
| Karnofsky performance status | | |
| 100 | 383.0 (85.5) | 344.0 (80.4) |
| 90 | 57.0 (12.7) | 67.0 (15.7) |
| 80 | 8.0 (1.8) | 17.0 (4.0) |
| Menopausal status at diagnosis | | |
| Premenopausal | 136.0 (30.4) | 140.0 (32.7) |
| Postmenopausal | 312.0 (69.6) | 288.0 (67.3) |
| Histologic type | | |
| Invasive ductal carcinoma | 395.0 (88.2) | 369.0 (86.2) |
| Invasive lobular carcinoma | 9.0 (2.0) | 10.0 (2.3) |
| Other | 44.0 (9.8) | 49.0 (11.4) |
| Histologic grade | | |
| G1 | 15.0 (3.3) | 12.0 (2.8) |
| G2 | 82.0 (18.3) | 81.0 (18.9) |
| G3 | 323.0 (72.1) | 299.0 (69.9) |
| GX | 28.0 (6.3) | 36.0 (8.4) |
| Phenotype by IHC | | |
| Basal ^a | 329.0 (7,373.4) | 318.0 (7,474.3) |
| Nonbasal | 119.0 (2,626.6) | 110.0 (2,525.7) |
| Stage at diagnosis (AJCC 2002) | | |
| I | 62.0 (13.8) | 74.0 (17.3) |
| II | 270.0 (60.3) | 271.0 (63.3) |
| III | 106.0 (23.7) | 80.0 (18.7) |
| Not available | 10.0 (2.2) | 3.0 (0.7) |
| Nodal status | | |
| Negative | 244.0 (54.5) | 242.0 (56.5) |
| 1-3 positive nodes | 121.0 (27.0) | 124.0 (29.0) |
| ≥ 4 positive nodes | 77.0 (17.2) | 61.0 (14.3) |
| Missing data | 6.0 (1.3) | 1.0 (0.2) |
| Type of prior chemotherapy | | |
| Adjuvant (only) | 353.0 (78.8) | 352.0 (82.2) |
| Neoadjuvant (± adjuvant) | 89.0 (19.9) | 75.0 (17.5) |
| Missing data | 6.0 (1.3) | 1.0 (0.2) |

(continued on following page)

nodes—according to the American Joint Committee on Cancer 2002 staging system. Patients without axillary node involvement (NO) were also eligible provided the primary tumor measured 1 cm or greater in diameter. Patients were ineligible in the case of bilateral invasive breast cancer, absence of surgical treatment with curative intent, resection of fewer than 6 lymph nodes when axillary lymph node dissection was performed, or pregnancy or breastfeeding. Triple-negative and basal versus nonbasal status were determined centrally by a GEICAM Spanish Breast Cancer Group pathologist (F.R.). Tumors with any staining for epidermal growth factor receptor and/or cytokeratins 5/6 were considered basal. Patients with no staining for both biomarkers were considered nonbasal.³

Study Procedures

Baseline assessments performed before patient randomization in centrally confirmed eligible patients included mammography, chest radiography, abdominal ultrasonography and/or computed tomography (CT), bone scan (if bone pain or increased alkaline phosphatase), and bone X-ray (if suspicious lesions on the bone scan). Hematology, biochemistry, and pregnancy test—potentially fertile women only—were also completed before randomization.

Eligible patients were stratified according to basal status (yes v no), institution, number of axillary lymph nodes (0 v 1-3 v 4 or more), and type of adjuvant chemotherapy (anthracyclines plus taxanes v anthracyclines alone). Patients were randomly assigned on a one-to-one basis to eight cycles of capecitabine 2,000 mg/m² (1,000 mg/m² administered orally two times per day) on days 1 to 14 every 3 weeks, or observation. Two dose reductions were permitted—75% and 50% of initial dose—on the basis of hematologic or nonhematologic adverse events (AEs) observed. Randomization was centralized at GEICAM headquarters.

AEs were assessed during the study period and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Serious AEs (SAEs) were reported during the study treatment and within 30 days of the end of this time period.

Physical examination, menopausal status, and presence of amenorrhea were assessed at baseline, at every cycle during the treatment period, every 3 months during years 1 to 2, every 6 months during years 3 to 5, and yearly afterward. Mammograms were performed yearly. Chest X-ray, abdominal ultrasounds, CT scan, or bone scans were performed if clinically indicated in the case of suspicion of disease recurrence. A complete follow-up on vital status was obtained until April 11, 2018, for all patients.

Statistical Analysis

Primary end point was disease-free survival (DFS), which was measured from the date of random assignment in the intent-to-treat (ITT) population to locoregional or distant

TABLE 1. Patients' Demographics and Baseline Disease Characteristics According to Study Arm (intention-to-treat population) (continued)

| Demographic or Characteristic | Capecitabine Arm (n = 448), No. (%) | Observation Arm (n = 428), No. (%) |
|--|--|---------------------------------------|
| pCR in patients with neoadjuvant chemotherapy ^b | 22.0 (24.7) | 19.0 (25.3) |
| Chemotherapy regimen | | |
| Anthracyclines based | 147.0 (32.8) | 138.0 (32.2) |
| Anthracyclines and taxanes based | 301.0 (67.2) | 290.0 (67.8) |
| Breast surgery | | |
| Conservative | 237.0 (52.9) | 242.0 (56.5) |
| Mastectomy | 205.0 (45.8) | 185.0 (43.2) |
| Missing data | 6.0 (1.3) | 1.0 (0.2) |
| Axillary surgery | | |
| ALND ± SLNB | 349.0 (78.0) | 306.0 (71.5) |
| SLNB | 99.0 (22.1) | 122.0 (28.5) |
| Radiation therapy | | |
| Yes | 352.0 (78.6) | 346.0 (80.8) |
| No | 91.0 (20.3) | 81.0 (18.9) |
| Unknown | 5.0 (1.1) | 1.0 (0.2) |

NOTE. Data are presented as No. (%) except where otherwise noted.

Abbreviations: AJCC, American Joint Committee on Cancer; ALND, axillary lymph node dissection; IHC, immunohistochemistry; pCR, pathologic complete response; SLNB, sentinel lymph node biopsy.

^aBasal phenotype: cytokeratins 5/6-positive and/or epidermal growth factor receptor positive.

^bpCR in the breast and ipsilateral axilla.

recurrence, second primary malignancy, or death date, whichever occurred first. Secondary end points included 5-year DFS, overall survival (OS), safety, and analyses by subgroups and of biomarkers.

According to the GEICAM El Álamo registry,⁴ estimated 5-year DFS for a similar population of patients with TNBC was 64.7%. The aim was to detect an increase in DFS to 73.7% with capecitabine, corresponding to a hazard ratio (HR) of 0.701 with a power of 80% using a two-tailed log-rank test at 0.05 and considering 4 years of recruitment and 3 years of follow-up. Two hundred fifty-five events were projected and 834 eligible patients were needed. Assuming a drop-out rate of 5%, 876 patients were to be enrolled—438 patients in each arm. The sample size calculation was performed using EAST version 5.2.

The initial protocol established the main DFS analysis to be performed after 255 events; however, the number of DFS events was much lower than expected and the steering committee of the study—with the advice of the independent data monitoring committee—therefore decided to perform the analysis after a median follow-up of more than 7 years after a total of 225 events and when the rate of annual recurrences was low in both arms of the study.

We used the Kaplan-Meier limit-product method to estimate DFS and OS and comparison between the two study arms was performed using the stratified log-rank test using the stratification factors [basal status, number of axillary lymph nodes, and type of (neo)adjuvant chemotherapy]. All tests of hypotheses were two sided. In addition, we performed a multivariable Cox proportional hazard model analysis for DFS and OS to adjust for major prognostic factors: age, menopausal status, histopathologic findings, tumor size, disease stage, type of surgery, region, and the stratification factors for randomization.

The safety analysis was performed in all patients who had received at least 1 cycle of study treatment. The worst AE grade per category for each patient was reported.

RESULTS

Study Patients

Between October 2006 and September 2011, 876 patients were recruited across 80 institutions in 8 countries (Spain, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, and Venezuela; Fig 1).

Demographics and baseline disease characteristics were balanced, with no statistical differences between the two arms but with a slightly numerically higher proportion of poor prognosis features in the capecitabine arm (Table 1). The majority of patients were white and postmenopausal, and median age was 49 years. Most frequently, tumors were of grade 3 (71%), basal phenotype (73.9%), stage II at diagnosis (61.8%), and node negative (55.9%). Small differences were found in relation to disease stage at diagnosis—based on American Joint Committee on Cancer 2002—and the number of involved lymph nodes.

Most patients in both arms had received adjuvant chemotherapy with anthracyclines and taxanes (67.5%), had breast-conservative surgery (54.7%) and axillary lymph node dissection with or without sentinel lymph node biopsy (74.8%), and received radiation therapy (79.7%).

Drug Exposure and Discontinuations

Of patients who were assigned to capecitabine, 75.2% (n = 337) completed 8 cycles of treatment. Median number of cycles was 8 (range, 1 to 8 cycles). A few patients (n = 12; 2.7%) did not complete at least 1 cycle of treatment and were excluded from the safety analysis as per protocol requirement. Four percent (n = 18) of patients completed 1 cycle of capecitabine, 10.3% (n = 46) of patients completed 2 to 4 cycles, and 7.8% (n = 35) of patients completed 5 to 7 cycles. Median dose intensity was 86.3% (range, 0.86% to 136.2%). Dose intensity rate was between 110% and 80% in 55.8% (n = 250) of patients and less than 75% in 33.5% (n = 150) of patients. Five patients were reported to have a dose intensity rate between 110% and 136.2%. In four of these patients, it was because of a mistake or rounding the capecitabine dose and in the

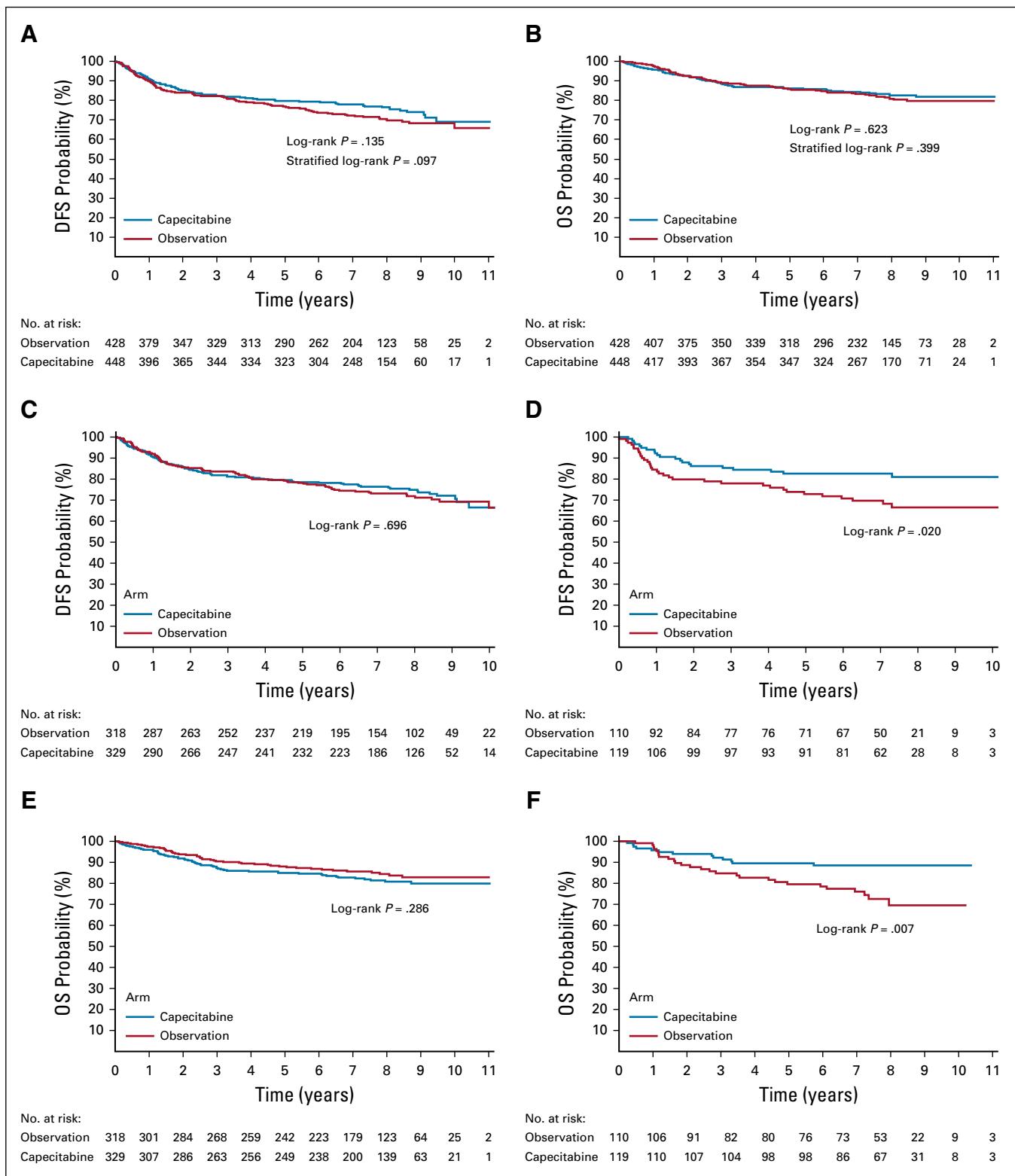


FIG 2. (A, C, D) Disease-free survival (DFS) and (B, E, F) overall survival (OS) Kaplan-Meier curves on the intention-to-treat population and subpopulations based on the immunohistochemistry phenotype.

fifth patient the reason is unknown. Dose reductions of capecitabine were reported in 161 patients (36.9%).

Main reasons for discontinuation of capecitabine ($n = 97$) were patient refusal, unacceptable toxicity, disease recurrence, or interruption of capecitabine for more than 3 weeks because of AEs (Fig 1).

Efficacy

At the time of data cutoff, median follow-up was 7.4 years and 7.2 years in the capecitabine and observation arms, respectively. A total of 225 events were observed, 105 (23.4%) in the capecitabine arm and 120 (28%) in the observation arm. In the ITT analysis ($n = 876$), results of the Cox proportional hazards regression model did not demonstrate a statistically significant difference in DFS between the capecitabine and observation arms (unadjusted HR, 0.82; 95% CI, 0.63 to 1.06; $P = .136$; adjusted HR according to stratification factors, 0.79; 95% CI, 0.61 to 1.03; $P = .082$; and fully adjusted HR, 0.77; 95% CI, 0.59 to 1.00; $P = .051$). Five-year DFS rates were 79.6% (95% CI, 75.8% to 83.4%) in the capecitabine arm and 76.8% (95% CI, 72.7% to 80.9%) in the observation arm. Figure 2A shows the Kaplan-Meier curves for DFS. In addition, there was no statistically significant difference in

OS between study arms (unadjusted HR, 0.92; 95% CI, 0.66 to 1.28; $P = .623$; adjusted HR according to stratification factors, 0.88; 95% CI, 0.64 to 1.23; $P = .4562$; and fully adjusted HR, 0.86; 95% CI, 0.6262 to 1.20; $P = .371$). Five-year OS rates were 86.2% (95% CI, 82.9% to 89.4%) in the capecitabine arm and 85.9% (95% CI, 82.4% to 89.3%) in the observation arm. Figure 2B shows the Kaplan-Meier curves for OS.

An exploratory subgroup analysis for DFS in the ITT population (Fig 3) showed similar treatment effects by menopausal status (pre- v postmenopausal), phenotype (basal v nonbasal), nodal status (negative v 1 to 3 positive nodes, 4 or more positive nodes), type of previous CT scan (neoadjuvant v adjuvant), prior administration of taxanes (yes v no) and region (Spain v Latin America). Patients with a nonbasal phenotype had a statistically significant increase in DFS (HR, 0.53; 95% CI, 0.31 to 0.91; $P = .022$) and OS (HR, 0.42; 95% CI, 0.21 to 0.81; $P = .0095$) with capecitabine. Five-year DFS rates were 82.6% (95% CI, 75.7% to 89.5%) with capecitabine and 72.9% (95% CI, 64.4% to 81.3%) in the observation arm. Five-year OS rates were 89.5% (95% CI, 83.9% to 95.1%) with capecitabine and 79.6% (95% CI, 71.7% to 87.4%) in the observation arm. The interaction tests treatment/nonbasal status had

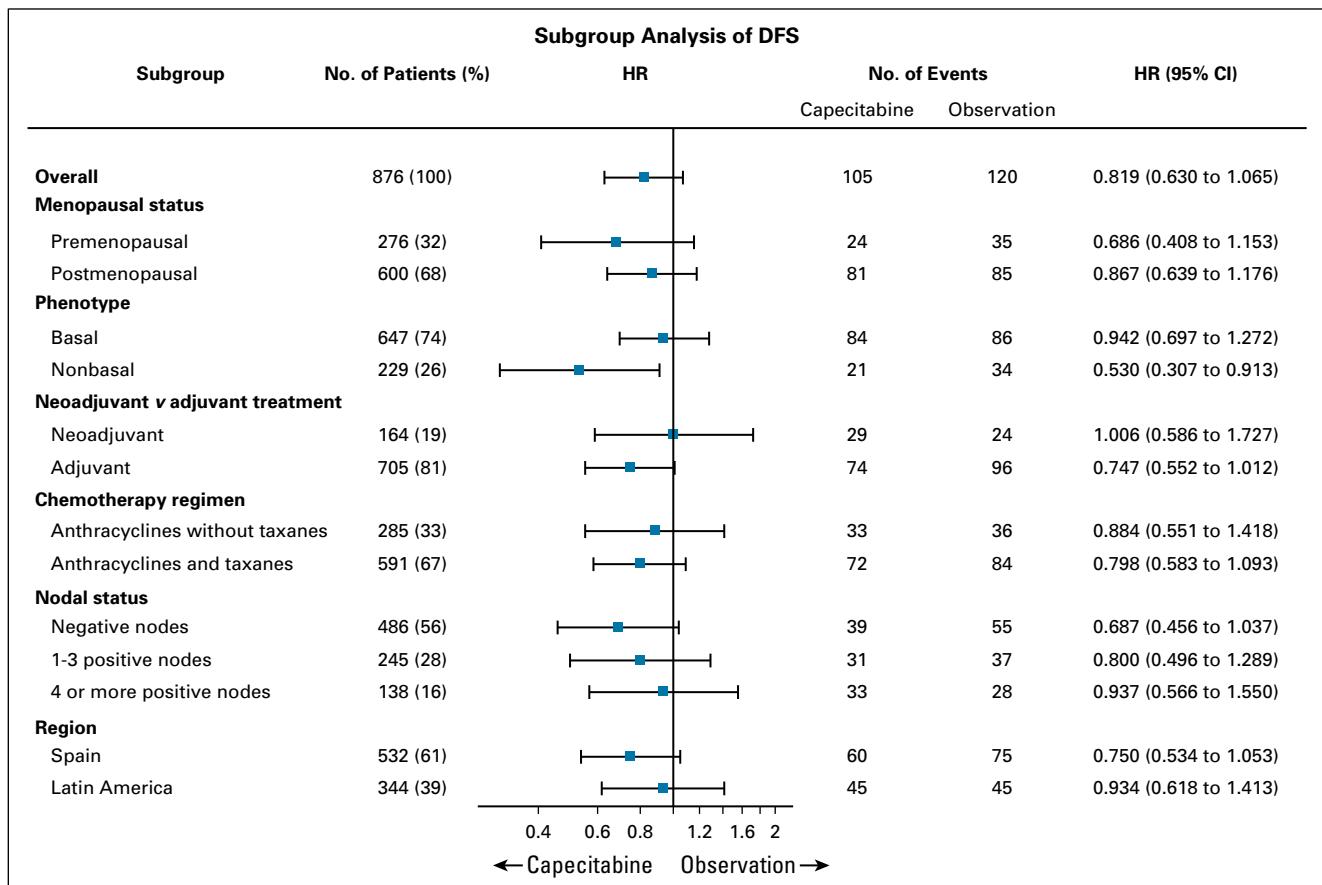


FIG 3. Subgroup analysis for disease-free survival (DFS) on the intention-to-treat (ITT) population. HR, hazard ratio.

TABLE 2. Disease-Free Survival Events in Overall Population (intention to treat) and Nonbasal Phenotype Subpopulation

| Variable | Overall Population, No. (%) | | Nonbasal Population, No. (%) | |
|---|-----------------------------|-----------------------|------------------------------|-----------------------|
| | Capecitabine (n = 448) | Observation (n = 428) | Capecitabine (n = 119) | Observation (n = 110) |
| Event | | | | |
| No event | 343.0 (76.6) | 308.0 (72.0) | 98.0 (82.4) | 76.0 (69.1) |
| Disease recurrence | 78.0 (17.4) | 94.0 (22.0) | 18.0 (15.1) | 24.0 (21.8) |
| Death | 14.0 (3.1) | 10.0 (2.3) | 2.0 (1.7) | 3.0 (2.7) |
| Second primary malignancy | 13.0 (2.9) | 16.0 (3.7) | 1.0 (0.8) | 7.0 (6.4) |
| Type of event | | | | |
| Any DFS event | 105.0 (23.4) | 120.0 (28.0) | 21.0 (17.6) | 34.0 (30.9) |
| Distant recurrence (any) | 64.0 (14.3) | 66.0 (15.4) | 13.0 (10.9) | 18.0 (16.4) |
| Contralateral invasive breast cancer | 12.0 (2.7) | 14.0 (3.3) | 3.0 (2.5) | 2.0 (1.8) |
| Ipsilateral breast cancer recurrence | 5.0 (1.1) | 12.0 (2.8) | 2.0 (1.7) | 3.0 (2.7) |
| Locoregional invasive recurrence (after mastectomy) | 0.0 | 4.0 (0.9) | 0.0 | 2.0 (1.8) |
| Regional invasive recurrence (after BCS) | 3.0 (0.7) | 1.0 (0.2) | 0.0 | 0.0 |
| Disease recurrence (unknown location) | 1.0 (0.2) | 0.0 | 0.0 | 0.0 |
| Second primary malignancy (nonbreast) | 6.0 (1.3) | 13.0 (3.0) | 1.0 (0.8) | 6.0 (5.5) |
| Death | 14.0 (3.1) | 10.0 (2.3) | 2.0 (1.7) | 3.0 (2.7) |
| Location of distant recurrence | | | | |
| Lung | 31.0 (6.9) | 29.0 (6.8) | 7.0 (5.9) | 6.0 (5.5) |
| Bone | 19.0 (4.2) | 19.0 (4.4) | 4.0 (3.4) | 5.0 (4.5) |
| Lymph nodes | 16.0 (3.6) | 18.0 (4.2) | 1.0 (0.8) | 4.0 (3.6) |
| Liver | 13.0 (2.9) | 20.0 (4.7) | 2.0 (1.7) | 6.0 (5.5) |
| CNS | 13.0 (2.9) | 15.0 (3.5) | 3.0 (2.5) | 6.0 (5.5) |
| Skin | 2.0 (0.4) | 0.0 | 0.0 | 0.0 |
| Brain | 2.0 (0.4) | 1.0 (0.2) | 0.0 | 0.0 |
| Other | 9.0 (2.0) | 12.0 (2.8) | 2.0 (1.7) | 3.0 (2.7) |

NOTE. The location of distant recurrence is not exclusive. Patients may have several organs involved as part of their distant recurrence.

Abbreviations: BCS, breast-conserving surgery; DFS, disease-free survival.

adjusted *P* values of .0694 for DFS and .0052 for OS. Figures 2C and 2D show the Kaplan-Meier curves for DFS and OS, respectively, in the basal and nonbasal phenotype subpopulations.

The number and type of DFS events in the overall and nonbasal populations are shown in Table 2. Of note, in the nonbasal subpopulation, and in agreement with DFS and OS data, DFS events were more frequent in the observation arm [30.9% (*n* = 34)] compared with the capecitabine arm [17.6% (*n* = 21)]. Remarkably, in this subtype the reduction of DFS events with capecitabine was mainly a result of distant relapses, particularly in liver, CNS, and lymph nodes. Demographics and baseline disease characteristics according to basal versus nonbasal phenotype are included in Table 3.

Safety

Safety was assessed in 861 patients of the study population: 436 patients (97.3%) in the capecitabine arm and

425 patients (99.3%) in the observation arm. AEs were reported in 95.4% (*n* = 416) of patients in the capecitabine arm and 63.8% (*n* = 271) in the observation arm (Table 4). In addition, 40.6% (*n* = 177) and 15.5% (*n* = 66) of patients had AEs of grade 3 or greater in the capecitabine and observation arms, respectively. With capecitabine, 92.4% (*n* = 403) of patients had AEs related to study treatment, and in 30% (*n* = 131) of patients these AEs were of grade 3 or greater. Patients who experienced at least one SAE were 5.3% (*n* = 23) in the capecitabine arm and 1.4% (*n* = 6) in the observation arm. In addition, there were a few patients with SAEs that caused death: 1.1% (*n* = 5) in the capecitabine arm and 0.5% (*n* = 2) in the observation arm. Two deaths in the capecitabine arm were probably related to study treatment according to investigator's criteria. These SAEs included one case of septic shock in the absence of neutropenia and one case of grade 4 hyperbilirubinemia and systemic organ failure.

TABLE 3. Patients' Demographics and Baseline Disease Characteristics According to Basal Versus Nonbasal Phenotype (intention-to-treat population)

| Demographic or Characteristic | Capecitabine, No. (%) | | Observation, No. (%) | |
|--|---|--|---|--|
| | Basal ^a Phenotype (n = 329) | Nonbasal ^a Phenotype (n = 119) | Basal ^a Phenotype (n = 318) | Nonbasal ^a Phenotype (n = 110) |
| Median age, years (range) | 50.0 (24.0-79.0) | 50.0 (20.0-75.0) | 49.0 (26.0-82.0) | 48.0 (23.0-74.0) |
| Region | | | | |
| Spain | 202.0 (61.4) | 70.0 (58.8) | 189.0 (59.4) | 71.0 (64.5) |
| Latin America | 127.0 (38.6) | 49.0 (41.2) | 129.0 (40.6) | 39.0 (35.5) |
| Menopausal status at diagnosis | | | | |
| Premenopausal | 105.0 (31.9) | 31.0 (26.1) | 107.0 (33.6) | 33.0 (30.0) |
| Postmenopausal | 224.0 (68.1) | 88.0 (73.9) | 211.0 (66.4) | 77.0 (70.0) |
| Histologic grade | | | | |
| G1 | 10.0 (3.0) | 5.0 (4.2) | 9.0 (2.8) | 3.0 (2.7) |
| G2 | 62.0 (18.8) | 20.0 (16.8) | 55.0 (17.3) | 26.0 (23.6) |
| G3 | 238.0 (72.3) | 85.0 (71.4) | 235.0 (73.9) | 64.0 (58.2) |
| GX | 19.0 (5.8) | 9.0 (7.6) | 19.0 (6.0) | 17.0 (15.5) |
| Stage at diagnosis (AJCC 2002) | | | | |
| I | 50.0 (15.2) | 12.0 (10.1) | 59.0 (18.6) | 15.0 (13.6) |
| II | 201.0 (61.1) | 69.0 (58.0) | 200.0 (62.9) | 71.0 (64.5) |
| III | 73.0 (22.2) | 33.0 (27.7) | 56.0 (17.6) | 24.0 (21.8) |
| Not available | 5.0 (1.5) | 5.0 (4.2) | 3.0 (0.9) | 0.0 |
| Nodal status | | | | |
| Negative | 179.0 (54.4) | 65.0 (54.6) | 187.0 (58.8) | 55.0 (50.0) |
| 1-3 positive nodes | 90.0 (27.4) | 31.0 (26.1) | 88.0 (27.7) | 36.0 (32.7) |
| ≥ 4 positive nodes | 57.0 (17.3) | 20.0 (16.8) | 42.0 (13.2) | 19.0 (17.3) |
| Missing data | 3.0 (0.9) | 3.0 (2.5) | 1.0 (0.3) | 0.0 |
| Type of prior chemotherapy | | | | |
| Adjuvant (only) | 273.0 (83.0) | 80.0 (67.2) | 269.0 (84.6) | 83.0 (75.5) |
| Neoadjuvant (± adjuvant) | 53.0 (16.1) | 36.0 (30.3) | 48.0 (15.1) | 27.0 (24.5) |
| Missing data | 3.0 (0.9) | 3.0 (2.5) | 1.0 (0.3) | 0.0 |
| pCR in patients with neoadjuvant chemotherapy ^b | 12.0 (22.6) | 10.0 (27.8) | 12.0 (25.0) | 7.0 (25.9) |
| Chemotherapy regimen | | | | |
| Anthracyclines based | 118.0 (35.9) | 29.0 (24.4) | 109.0 (34.3) | 29.0 (26.4) |
| Anthracyclines and taxanes based | 211.0 (64.1) | 90.0 (75.6) | 209.0 (65.7) | 81.0 (73.6) |

NOTE. Data are presented as No. (%) except where otherwise noted.

Abbreviations: AJCC, American Joint Committee on Cancer; pCR, pathologic complete response.

^aBasal phenotype: cytokeratins 5/6 positive and/or epidermal growth factor receptor positive; and nonbasal phenotype: cytokeratins 5/6 and epidermal growth factor receptor negative.

^bpCR in the breast and ipsilateral axilla.

DISCUSSION

Our study failed to show a statistically significant improvement in DFS by adding 8 cycles of extended capecitabine to standard (neo)adjuvant chemotherapy for operable TNBC after a median follow-up of more than 7 years. Adjusted HR, considering the stratification factors, was 0.79 ($P = .082$); therefore, the study was formally negative in accordance with the statistical assumption made when the trial was designed. The role of capecitabine

in combination with other drugs as adjuvant therapy of operable breast cancer is still unclear.⁵⁻⁷ As a single agent, adjuvant capecitabine was inferior to standard adjuvant therapy—either cyclophosphamide, methotrexate, fluorouracil; or doxorubicin plus cyclophosphamide—in patients with breast cancer age 65 years or older.⁸ A recent meta-analysis of (neo)adjuvant capecitabine trials, including 8 trials and 9,302 patients, found that globally, capecitabine did not improve DFS⁹; however, in trials in which capecitabine

TABLE 4. Safety Profile According to Study Arm (safety population)

| AEs Based on NCI-CTCAE v3.0 (AEs reported in ≥ 5% globally) | Capecitabine Arm (n = 436), No. (%) | | | Observation Arm (n = 425), No. (%) | | |
|---|-------------------------------------|-------------|-----------|------------------------------------|-------------|---------|
| | Grade 1-4 | Grade 3 | Grade 4 | Grade 1-4 | Grade 3 | Grade 4 |
| Hand and foot syndrome | 306.0 (70.2) | 82.0 (18.8) | — | 3.0 (0.7) | — | — |
| Diarrhea | 154.0 (35.3) | 14.0 (3.2) | 1.0 (0.2) | 6.0 (1.4) | — | — |
| Nausea | 103.0 (23.6) | 4.0 (0.9) | — | 6.0 (1.4) | — | — |
| Vomiting | 45.0 (10.3) | 3.0 (0.7) | — | 2.0 (0.5) | — | — |
| Abdominal pain, general | 27.0 (6.2) | 1.0 (0.2) | — | 1.0 (0.2) | — | — |
| Any cardiac event, general | 5.0 (1.1) | 2.0 (0.5) | — | 4.0 (0.9) | 1.0 (0.2) | — |
| Fatigue | 172.0 (39.44) | 13.0 (3.0) | — | 48.0 (11.3) | — | — |
| Irregular menses | 69.0 (15.8) | 57.0 (13.1) | — | 67.0 (15.8) | 55.0 (12.9) | — |
| Hemoglobin decrease | 107.0 (24.5) | 1.0 (0.2) | — | 27.0 (6.4) | — | — |
| Leukocytes (total WBC) decrease | 136.0 (31.2) | 1.0 (0.2) | — | 58.0 (13.6) | — | — |
| Lymphopenia | 63.0 (14.4) | 3.0 (0.7) | 1.0 (0.2) | 33.0 (7.8) | 1.0 (0.2) | — |
| Neutrophils/granulocytes decrease | 125.0 (28.7) | 8.0 (1.8) | — | 46.0 (10.8) | — | — |
| Thrombocytopenia | 22.0 (5.0) | 1.0 (0.2) | — | 8.0 (1.9) | — | — |
| ALT, SGPT increase | 85.0 (19.5) | 1.0 (0.2) | — | 28.0 (6.6) | — | — |
| AST, SGOT increase | 83.0 (19.0) | — | 1.0 (0.2) | 23.0 (5.4) | — | — |
| Hyperbilirubinemia | 52.0 (11.9) | 2.0 (0.5) | 1.0 (0.2) | 2.0 (0.5) | — | — |
| Alkaline phosphatase increase | 63.0 (14.4) | — | — | 30.0 (7.1) | — | — |
| Hypercholesterolemia | 34.0 (7.8) | — | — | 35.0 (8.2) | — | — |
| Heartburn/dyspepsia | 53.0 (12.2) | — | — | 5.0 (1.2) | — | — |
| Nail changes | 42.0 (9.6) | 2.0 (0.5) | — | 3.0 (0.7) | — | — |
| Sensory neuropathy | 66.0 (15.1) | 3.0 (0.7) | — | 25.0 (5.9) | 1.0 (0.2) | — |
| Musculoskeletal pain (joint) | 54.0 (12.4) | 1.0 (0.2) | — | 29.0 (6.8) | 1.0 (0.2) | — |
| Musculoskeletal pain (muscle) | 39.0 (8.9) | 1.0 (0.2) | — | 9.0 (2.1) | — | — |
| Headache | 43.0 (9.9) | — | — | 7.0 (1.6) | — | — |

Abbreviations: AE, adverse event; NCI-CTCAE v3.0, National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

was added to standard adjuvant chemotherapy (in contrast to those trials in which capecitabine replaced standard agents), a significant DFS advantage was found. Of note, in this meta-analysis the benefit of adding capecitabine to standard chemotherapy was mainly observed in patients with TNBC. The GEICAM-CIBOMA study added sequential capecitabine to standard (neo)adjuvant chemotherapy in patients with operable TNBC but was unable to show a statistically significant improvement in DFS in the overall population. The results of our study were therefore apparently different from those of the meta-analysis and, in particular, from those of the the Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial,¹⁰ which addressed a similar question but in a population at higher risk of relapse. The CREATE-X trial randomly assigned patients with breast cancer with residual disease at surgery after standard neoadjuvant chemotherapy to 6 to 8 cycles of capecitabine versus observation—plus hormone therapy in both arms for patients with hormone receptor-positive tumors—and found a statistically significant increase in

DFS and OS with capecitabine. The effect was particularly remarkable in TNBC. Compared with our trial, the populations in both studies were significantly different, as Asian patients had a significantly higher risk of relapse, as shown by the 56.1% 5-year DFS for patients with TNBC in the control arm of the CREATE-X trial. In contrast, DFS in the control arm in our trial was better than expected: DFS at 5 years was 76.8%, while our statistical hypothesis assumed a 5-year DFS of 64.7% on the basis of historical controls.

Moreover, the selection criteria in the CREATE-X trial limited to patients with residual disease after neoadjuvant treatment suggest that capecitabine could have a more relevant role in patients with tumors that are less sensitive or partially resistant to regimens containing anthracyclines and taxanes.

The DFS events in our trial were numerically higher in the control group (n = 120) than in the capecitabine group (n = 105), arguably because of the apparent efficacy of

capecitabine in a predefined subgroup of patients—being a stratification factor as well—with nonbasal phenotype, as defined by central immunohistochemistry (lack of staining for epidermal growth factor receptor and cytokeratins 5/6). In these patients, both DFS and OS were statistically superior with capecitabine. TNBC is a heterogeneous disease that encompasses a wide spectrum of clinical and molecular subtypes with different sensitivity to standard therapies.¹¹ The results in the nonbasal subgroup suggest that the activity of capecitabine might be selective for this particular subset of patients, although a validation of this hypothesis in other TNBC adjuvant trials exploring capecitabine is necessary to confirm the finding. Perhaps capecitabine is less effective in basal-like tumors as these are highly proliferative tumors and more sensitive to taxanes carboplatin and eribulin, as seen in the TNT trial comparing docetaxel with carboplatin¹² and the 301 study comparing eribulin with capecitabine,¹³ whereas nonbasal tumors could be more sensitive to an antimetabolite drug, such as capecitabine, as they have a lower proliferation index.

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The tolerability of capecitabine was as expected, with a median dose intensity of 86.3% and 75.2% of patients receiving the planned 8 cycles of therapy.

Among the limitations of this trial, we can include the fact that it was an open-label study. In addition, the population enrolled demonstrated a much lower recurrence rate than expected. The latter finding has been observed in other recent adjuvant trials and compromises the ability to show a difference between treatment strategies. In contrast, designed in 2002 to 2003, this was one of the first trials, to our knowledge, devoted to this specific subtype of breast cancer.

In conclusion, the GEICAM-CIBOMA study failed to show a statistically significant improvement in DFS by adding capecitabine to standard (neo)adjuvant chemotherapy for operable TNBC. An apparent improvement in DFS and OS was observed in the nonbasal subset of patients, although the real implication of this finding should be further confirmed with the analysis of other (neo)adjuvant capecitabine trials.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Phase III Trial of Adjuvant Capecitabine After Standard Neo-/Adjuvant Chemotherapy in Patients With Early Triple-Negative Breast Cancer (GEICAM/2003-11_CIBOMA/2004-01)**

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