original article

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Differential efficacy of three cycles of CMF followed by tamoxifen in patients with ER-positive and ER-negative tumors: Long-term follow up on IBCSG Trial IX

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Background: The benefit of adjuvant chemotherapy in postmenopausal patients with estrogen receptor (ER)-positive lymph node-negative breast cancer is being reassessed.

Patients and methods: After stratification by ER status, 1669 postmenopausal patients with operable lymph node-negative breast cancer were randomly assigned to three 28-day courses of 'classical' CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy followed by tamoxifen for 57 months (CMF→tamoxifen) or to tamoxifen alone for 5 years.

Results: ERs were positive in 81% of tumors. At a median follow-up of 13.1 years, patients with ER-positive breast cancers did not benefit from CMF [13-year disease-free survival (DFS) 64% CMF→tamoxifen, 66% tamoxifen; $P = 0.99$], whereas CMF substantially improved the prognosis of patients with ER-negative breast cancer (13-year DFS 73% versus 57%, $P = 0.001$). Similarly, breast cancer-free interval (BCFI) was identical in the ER-positive cohort but significantly improved by chemotherapy in the ER-negative cohort (13-year BCFI 80% versus 63%, $P = 0.001$). CMF had no influence on second nonbreast malignancies or deaths from other causes.

Conclusion: CMF is not beneficial in postmenopausal patients with node-negative ER-positive breast cancer but is highly effective within the ER-negative cohort. In the future, other markers of chemotherapy response may define a subset of patients with ER-positive tumors who may benefit from adjuvant chemotherapy.

Key words: adjuvant chemotherapy, breast cancer, estrogen receptor, postmenopause, tamoxifen

introduction

In recent years, the use of adjuvant chemotherapy in women with node-negative postmenopausal breast cancer has been increasingly questioned, and the identification of patients who might be spared chemotherapy is one of the current priorities of clinical research [1]. While RNA expression-based multigene markers have the potential to identify patients who benefit from chemotherapy [2], they are not universally available because of substantial cost to consumers and because of logistic issues in many countries; in addition, while retrospective analyses of the performance of such tests are promising, they have not yet been proven useful in randomized prospective trials. In contrast, the determination of estrogen receptors (ERs) by immunohistochemistry is very widely available worldwide and was found to predict the efficacy of chemotherapy [3–5]. The International Breast Cancer Study Group (IBCSG) Trial IX, a prospective randomized controlled clinical trial of endocrine versus

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chemoendocrine therapy in women with postmenopausal node-negative breast cancer, found that the substantial benefit of chemotherapy with oral cyclophosphamide, methotrexate and fluorouracil (CMF) was limited to patients with low or absent ER expression; patients with ER-positive breast cancer did not benefit from chemotherapy at a median follow-up of 5.9 years [6]; similar findings were reported by other collaborative groups [7]. The present report updates IBCSG Trial IX at 13.1 years median follow-up, comparing adjuvant endocrine with chemoendocrine therapy according to ER expression.

patients and methods

The design of IBCSG Trial IX and the patient population have been described in a prior report [6]. In 1988, tamoxifen was used in the adjuvant therapy of postmenopausal women irrespective of the ER status of the breast cancer, although some evidence pointed to a superior efficacy in patients with ER-positive tumors. Randomization was stratified according to ER status, and the intention to perform separate analysis according to ER status was specified in the original protocol. This analysis was limited to the 1646 eligible patients with known ER status of the 1715 randomized (Table 1).

All patients had histologically proven unilateral breast cancer of stage T1a to T3, pN0, M0, with either ER-positive or ER-negative primary tumors. Surgery of the primary tumor was either a total mastectomy or a breast-conserving procedure (quadrantectomy or lumpectomy); axillary lymph node dissection was mandatory. Radiation therapy was recommended for completing breast conservation and was postponed until the end of chemotherapy. Postmenopausal status was defined as having one of the following sets of characteristics: (i) older than 52 years with at least 1 year of amenorrhea; (ii) 52 years old or younger with at least 3 years of amenorrhea; (iii) 56 years old or older with hysterectomy but no bilateral oophorectomy; or (iv) biochemical evidence of cessation of ovarian function (for doubtful patients). Staging before randomization included chest X-ray, contralateral mammogram, bone scintigram (if clinically indicated), and hematological, liver, and renal function tests. Clinical, hematological, and biochemical assessments were required every 3 months for the first year, every 6 months for the second year, and yearly thereafter. Mammography was carried out yearly.

A joint analysis of two randomized trials comparing three with six cycles of CMF chemotherapy in patients with node-positive breast cancer revealed similar survival outcomes with markedly less toxicity in patients receiving three cycles [8]. Therefore, after stratification by locally determined ER status, patients were randomly assigned to receive three 28-day courses of 'classical' adjuvant CMF chemotherapy (cyclophosphamide at 100 mg/m^2 on days 1–14, orally; methotrexate at 40 mg/m^2 on days 1 and 8, intravenously; and 5-fluorouracil at 600 mg/m^2 on days 1 and 8, intravenously) followed by tamoxifen (20 mg/day, orally for 57 months) (CMF→tamoxifen) or to receive tamoxifen alone (20 mg/day, orally for 60 months).

statistical methods

The comparisons between treatments were carried out on the intention-to-treat principle. End points of interest were disease-free survival (DFS), overall survival (OS), and breast cancer-free interval (BCFI). DFS was defined as the length of time from the date of randomization to any invasive breast cancer relapse (including ipsilateral or contralateral breast recurrence), the appearance of a second nonbreast malignancy, or death, whichever occurred first. OS was defined as the length of time from the date of randomization to death from any cause. BCFI was defined as the length of time from the date of randomization to any invasive breast cancer relapse (including ipsilateral or contralateral breast recurrence), according to the 'STEEP (Standardized Definitions for Efficacy End Points) System' [9] and was censored at date of last follow-up or at date of death without relapse.

DFS, OS, and BCFI percentages, standard errors, and treatment effect comparisons were estimated using the Kaplan–Meier method, Greenwood's formula, and log-rank tests, respectively. Cox proportional hazards regression models were used to control for prognostic features, to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for the treatment comparisons, and to test for interactions between potential prognostic factors and treatment effects.

Subpopulation treatment effect pattern plot (STEPP) analysis [10–12] was used to investigate the pattern of differences in 13-year DFS percentages

Table 1. Patient and tumor characteristics according to estrogen receptor (ER) status cohort

	Treatment assignment		
	Tamoxifen, *n* (%)	CMF→ tamoxifen, *n* (%)	Total, *n* (%)
ER-positive cohort	690	665	1355
Age (years)			
<55	116 (17)	122 (18)	238 (18)
55–59	179 (26)	184 (28)	363 (27)
60–64	204 (30)	166 (25)	370 (27)
>65	191 (28)	193 (29)	384 (28)
Surgical treatment			
Total mastectomy	323 (47)	332 (50)	655 (48)
Breast conservation	367 (53)	323 (50)	700 (52)
Tumor size (cm)			
≤1.0	74 (11)	89 (13)	163 (12)
1.1–2.0	341 (49)	325 (49)	666 (49)
>2	254 (37)	227 (34)	481 (36)
Unknown	21 (3)	24 (4)	45 (3)
Tumor grade			
1	144 (21)	133 (20)	277 (20)
2	312 (45)	307 (46)	619 (46)
3	196 (28)	182 (27)	378 (28)
Unknown	38 (6)	43 (6)	81 (6)
ER-negative cohort	145	146	291
Age (years)			
<55	34 (23)	30 (21)	64 (22)
55–59	27 (19)	37 (25)	64 (22)
60–64	40 (28)	39 (27)	79 (27)
>65	44 (30)	40 (27)	84 (29)
Surgical treatment			
Total mastectomy	87 (60)	76 (52)	163 (56)
Breast conservation	58 (40)	70 (48)	128 (44)
Tumor size (cm)			
≤1.0	15 (10)	9 (6)	24 (8)
1.1–2.0	52 (36)	58 (40)	110 (38)
>2	73 (50)	76 (52)	149 (51)
Unknown	5 (3)	3 (2)	8 (3)
Tumor grade			
1	1 (1)	3 (2)	4 (1)
2	40 (28)	27 (18)	67 (23)
3	94 (65)	111 (76)	205 (70)
Unknown	10 (7)	5 (3)	15 (5)

between treatment arms according to centrally determined quantitative ER value. Probability values for the interaction test of treatment and ER value were provided on the basis of simulations.

Cumulative incidence functions were estimated for each of the competing causes of failure: breast cancer recurrence, second nonbreast malignancy, and death without prior cancer event. Tests for differences between treatments were conducted by the method of Gray [13]. All probability values were obtained from two-sided tests.

ER assays

After the first publication of the trial, ER status was evaluated centrally by immunohistochemical assay for 1339 patients [14]. Centrally determined ER status was considered negative, if no ER staining (<1%) was detected in the neoplastic cells, and positive for any percentage of ER-positive cells. For 330 patients without central determination of ER status, locally evaluated ER status was used.

results

The median follow-up time of IBCSG Trial IX is 13.1 years. The baseline characteristics of the patients are summarized in Table 1. The median age was 60 years (range, 34–81). ERs were positive in 1355 primary tumors (81%), and 291 patients (17%) had primary ER-negative tumors. The median number of axillary lymph nodes examined was 16 (range, 5–47). Eighty-three percent of patients with breast-conserving surgery had adjuvant radiation therapy planned at the time of randomization.

efficacy

Three cycles of CMF chemotherapy did not benefit the patients with ER-positive breast cancer; 13-year DFS was 64% in patients with CMF followed by tamoxifen and 66% in patients treated with tamoxifen only (Figure 1, panel A). In these patients, OS and BCFI did not differ between the randomized groups (Figure 1, panels B and C). Similar results were found in multivariable analysis adjusting for age, tumor size, type of surgery, and histological grade.

CMF was very efficient in patients with ER-negative primaries reducing the risk of death or recurrence: 13-year DFS was 73% in patients treated with CMF followed by tamoxifen, whereas it was only 57% in patients who were randomized to receive tamoxifen alone (HR = 0.52; 95% CI 0.35–0.78; $P = 0.001$; Figure 1, panel D). BCFI was also improved significantly (13-year BCFI: 80% versus 63%; HR = 0.47; 95% CI 0.30–0.75; $P = 0.001$; Figure 1, panel F), but the absolute difference in 13-year OS survival of 10% (79% versus 69%) in favor of chemotherapy was not statistically significant (HR = 0.69; 95% CI 0.44–1.09; $P = 0.11$; Figure 1, panel E). This advantage was maintained after multivariable adjustment for age, tumor size, type of surgery, and histological grade (data not shown). The effect of CMF on DFS and BCFI was statistically significantly different for the two cohorts defined by ER status (tests for interaction: $P = 0.002$ for DFS, and $P = 0.006$ for BCFI); however, the effect on OS was not statistically significant (test for interaction: $P = 0.23$ for OS).

The interaction of treatment (CMF followed by tamoxifen versus tamoxifen alone) with ER expression as centrally quantified was further investigated in 1339 patients by STEPP methodology in terms of 13-year DFS percentages (Figure 2). Two-hundred and sixty-five patients had no ER expression by central review and they formed the first subpopulation of STEPP analysis. The subsequent overlapping subpopulations were formed by dropping the patients with the lowest values for ER and adding the patients with the next higher values of ER. It appears that only patients with no or a very low expression of ER benefit from adjuvant CMF.

long-term toxicity

Acute toxicity was described in detail in a previous report [6]. A cumulative incidence plot of the three competing causes of failure (breast cancer recurrence, second nonbreast malignancy, or death) according to ER status revealed that CMF chemotherapy had no influence on the incidence of second nonbreast malignancies or deaths without a cancer event (Figure 3). The types of second nonbreast malignancies and the causes of deaths without recurrence for all eligible patients are summarized in Supplemental Table S1 (available at *Annals of Oncology* online). Among patients in the two cohorts, 6.8% on CMF had a second nonbreast malignancy compared with 6.5% in the tamoxifen alone group, and deaths without prior cancer event were 7.2% and 5.9%, respectively.

discussion

Long-term follow-up after a median follow-up period of >13 years confirmed the findings of IBCSG Trial IX originally reported with 5.9 years of follow-up. Postmenopausal patients with ER-positive early breast cancer did not benefit from adjuvant therapy with three courses of oral cyclophosphamide, methotrexate, and fluorouracil (CMF) before tamoxifen, but patients with ER-negative breast cancer experienced substantial benefit; this replicates the observation reported for pre- and postmenopausal patients with so-called triple-negative breast cancers [15]. Three and six cycles yielded similar survival results in a joint analysis of two randomized controlled trials comparing longer with shorter chemotherapy [8]. National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-20, a randomized controlled trial comparing tamoxifen with CMF chemotherapy in combination with and followed by tamoxifen, used six cycles of CMF and reported no survival benefit of CMF in postmenopausal patients with node-negative ER-positive breast cancer [7]. Thus, it is unlikely that a longer CMF-containing chemotherapy would have generated a substantially different outcome in this patient population. The 13-year DFS in patients treated with CMF for ER-negative tumors was better than in the ER-positive cohort irrespective of the use of chemotherapy; OS and breast cancer-free interval were similar in patients with ER-positive tumors and in the ER-negative cohort treated with CMF.

Aromatase inhibitors are more effective agents than tamoxifen for prevention of local and distant recurrence [16]. The results of the present trial are therefore certainly applicable to contemporary adjuvant endocrine therapy incorporating aromatase inhibitors in postmenopausal patients.

ER expression was centrally determined by immunohistochemistry for most patients; the comparison

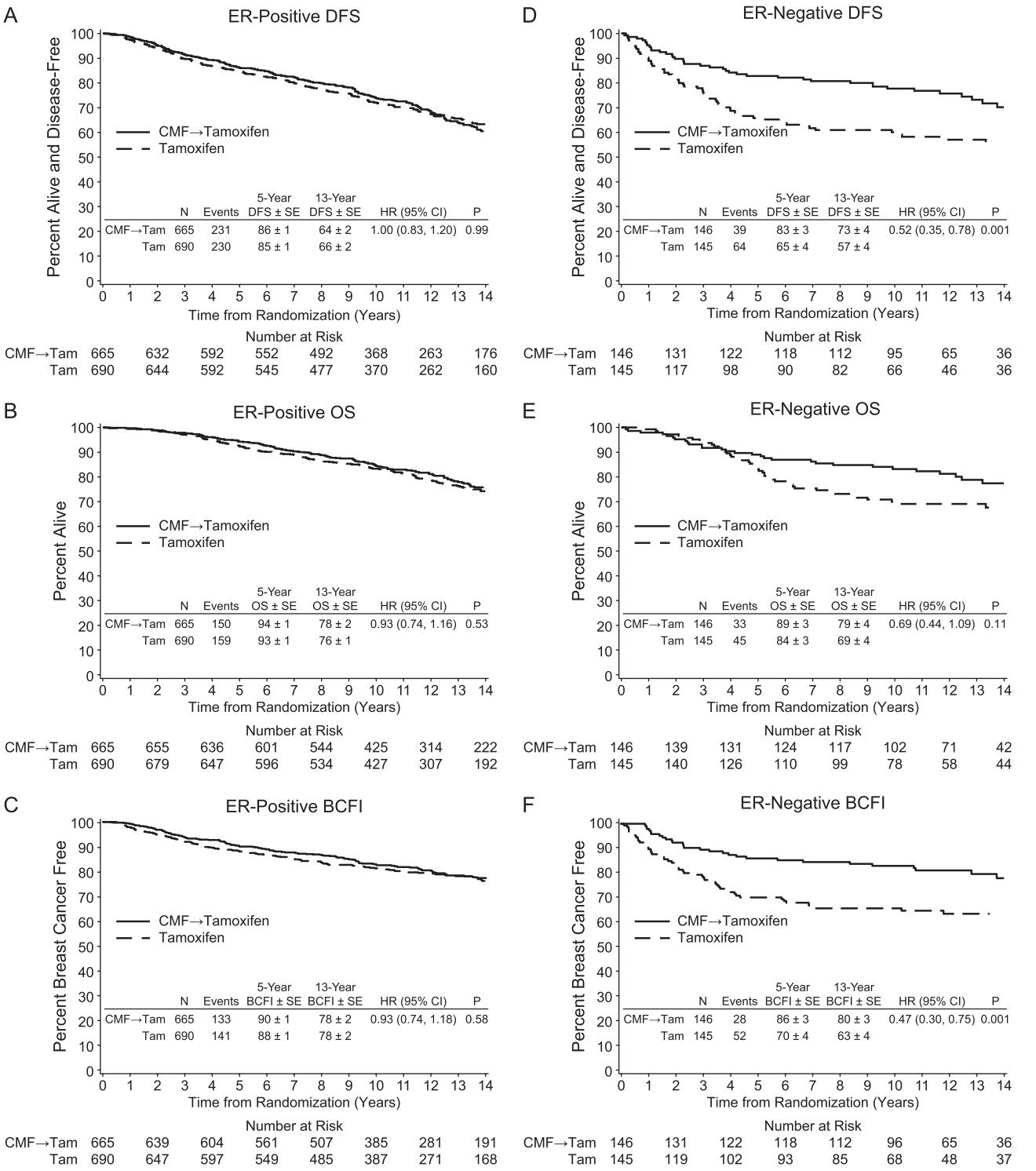

Figure 1. Kaplan–Meier plots for 1355 postmenopausal women with lymph node-negative breast cancer with estrogen receptor-positive [panel A, disease-free survival (DFS); panel B, overall survival (OS); panel C, breast cancer-free interval (BCFI)] and 291 women with estrogen receptor-negative (panel D, DFS; panel E, OS; panel F, BCFI) primary tumors at a median follow-up for 13.1 years.

between the traditional ligand-binding assay and the more recent immunohistochemistry yielded reasonably high rates of concordance (88%) between the methods, particularly when the methods were used to dichotomize the tumors into positive and negative with respect to ER expression [17]. Thus, the small number of patients for whom a central determination of ER status was not possible were assigned the correct ER status in most cases. Cellular ER content was found to be a predictor of response to tamoxifen and chemotherapy in NSABP B-20 [7] with patients whose cancers strongly express ER deriving no

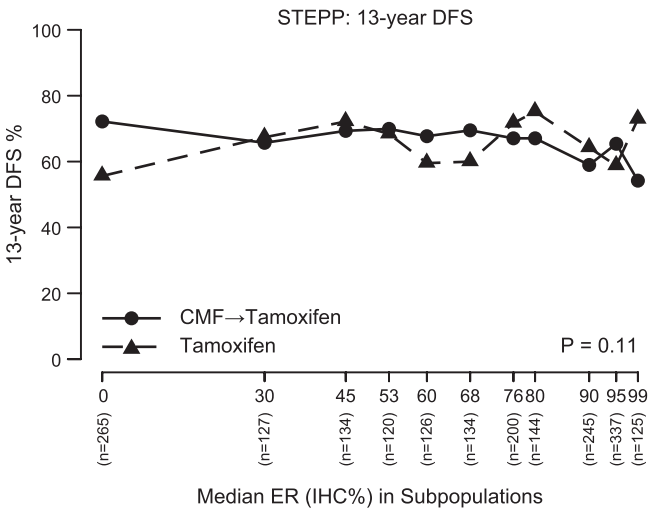

Figure 2. Subgroup Treatment Effect Patten Plot (STEPP) showing 13-year disease-free survival (DFS) percent according to centrally determined quantitative estrogen receptor (ER) values according to treatment assignment for 1339 patients. The *x*-axis is the median ER value for overlapping subpopulations.

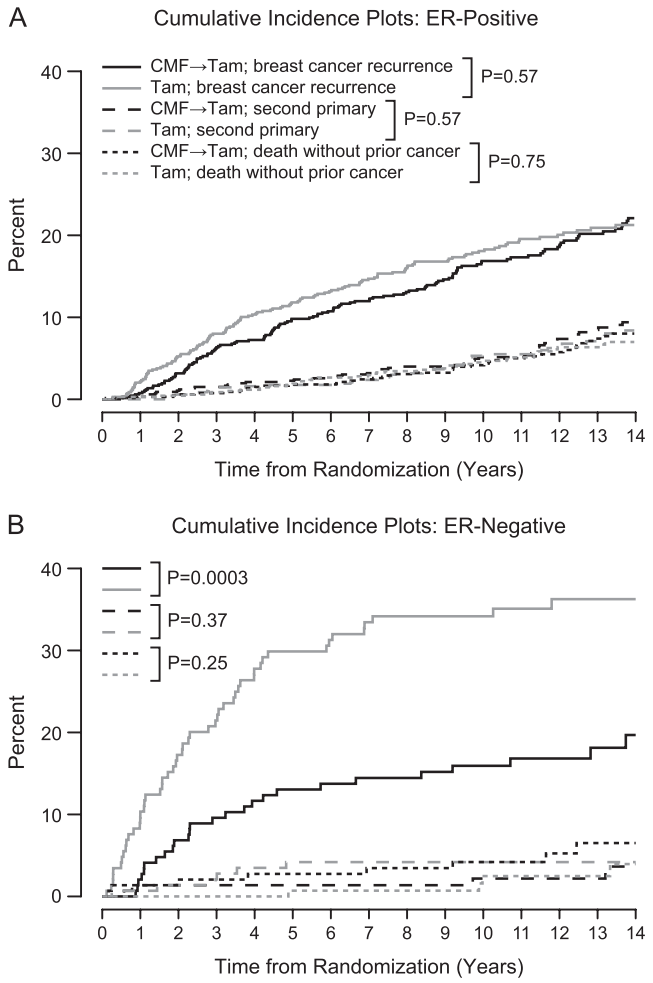

Figure 3. Cumulative incidence functions for breast cancer recurrence, second malignancy, and death without prior cancer event, for estrogen receptor (ER)-positive (panel A) and ER-negative (panel B) cohorts.

benefit from CMF chemotherapy. In the current trial, we observed no such pattern in the patients with ER-positive tumors [11].

Human epidermal growth factor receptor 2 (HER2) was not considered in the original trial. However, in a recent report with central review of HER2 in IBCSG trials VIII and IX Colleoni et al. observed no clear benefit of CMF in patients with ER-positive breast cancer [HR (CMF versus no CMF), 0.90, 95% CI 0.74–1.11] but a significant benefit in the triple-negative group (HR = 0.46, 95% CI 0.29–0.73). The magnitude of CMF efficacy seemed to be lower in the HER2-positive/endocrine receptor absent group (HR = 0.58, 95% CI 0.29–1.17) and in the small group of HER2-positive/endocrine receptor present group (n = 220, HR = 0.73, 95% CI 0.42–1.25) [15]. It is, therefore, unlikely that a separate analysis by ER and HER2 status could materially influence the interpretation of this trial.

Highly proliferating breast cancers tend to be more responsive to chemotherapy than tumors with few cycling cells [18–20]. Thus, the predictive value of Ki-67, a nuclear antigen expressed in proliferating cells, was investigated in participants of IBCSG IX. In contrast to certain other trials [19], centrally determined Ki-67 labeling index did not predict the efficacy of CMF chemotherapy relative to tamoxifen alone in the ER-positive cohort [21].

A multigene marker such as the Oncotype Dx Recurrence Score is a promising tool to identify patients who benefit from adjuvant CMF and anthracycline-based chemotherapies [2, 22]; however, the clinical utility of such tests still awaits confirmation in randomized controlled trials such as TAILORx [23] and MINDACT [24].

The results of long-term follow-up of IBCSG Trial IX do not hint toward a chemotherapy-induced overabundance of nonbreast neoplasias or non-cancer-related deaths. While OS of the CMF-treated patients was better in the original publication of Trial IX [6], this was no longer statistically significant. This observation is likely explained by the later occurrence of nonbreast cancer causes of death during long-term follow-up.

In summary, the present report confirms that three courses of classical CMF chemotherapy have no beneficial effect in postmenopausal women with lymph node-negative ER-positive breast cancer treated with adjuvant tamoxifen. In contrast, CMF is highly efficacious in postmenopausal women with ER-negative tumors.

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disclosure

The authors declare no conflict of interest.

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appendix

International Breast Cancer Study Group

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