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CIBOMA/2004−01: a randomised phase III trial assessing adjuvant capecitabine (X) maintenance therapy after standard chemotherapy for triple-negative early breast cancer (EBC)

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Background: A large adjuvant trial programme is exploring the role of X in EBC. The FinXX trial showed significantly improved recurrence-free survival when X was added to an anthracycline- and taxane-containing regimen. CIBOMA/2004−01 focuses on adjuvant X maintenance after conventional chemotherapy in triple-negative EBC.
Materials and Methods: Patients with operable, node-positive (or node-negative with tumour diameter $\geqslant$1 cm), hormone receptor-negative, HER2-negative EBC receive 6−8 cycles of standard anthracycline- and/or taxane-containing chemotherapy in the (neo)adjuvant setting (doxorubicin–cyclophosphamide $\times$4 allowed for node-negative disease), followed by radiotherapy if indicated. After central confirmation of immunohistochemistry status, patients are randomised to either 8 cycles of X (1000 mg/m^2 bid, d1−14 q21 d) or observation, stratified by centre, prior taxane (yes vs no), involved nodes (0 vs 1−3 vs $\geqslant$4) and phenotype (basal vs triple-negative). The primary endpoint is 5-year disease-free survival. Secondary endpoints include overall survival and safety. An optional pharmacogenetic substudy is exploring polymorphisms of thymidylate synthase and methylenetetrahydrofolate reductase in relation to efficacy and tolerability of X.
Results: To date, 405 patients from 8 countries have been randomised. Baseline characteristics are shown below. There have been only 7 serious adverse events considered possibly/probably related to X (hospitalisation for grade 2−4 diarrhoea in 3 patients; grade 2 thoracic pain, grade 2 arrhythmia, coronary vasospasm and chest pain in 1 patient each).

	X (n = 210)	Observation (n = 195)	P value
Median age, years (range)	51.3 (27−79)	49.2 (27−83)	0.139
Post menopausal, %	65.2	61.5	0.440
KPS, %			–
80	1.9	3.1	
90	14.8	14.3	
100	83.3	82.6	
No. of involved nodes, %			0.310
0	47.6	54.9	
1−3	32.9	29.7	
$\geqslant$4	19.5	15.4	
Standard chemotherapy, %			–
Anthracycline, no taxane	45.7	43.1	
Anthracycline + taxane	54.3	56.9	
Median tumour diameter, cm (range)	2.5 (0−11)	2.5 (0.8−9)	0.642
Grade, %			0.434
1	4.3	2.6	
2	21.0	21.5	
3	69.5	67.2	
Not assessable	5.2	8.7	
T stage, %			–
0	1.0	0.5	
1	29.9	27.7	
2	62.4	63.1	
3	6.7	8.2	
Unknown	0	0.5	
Histology, %			–
Ductal	89.1	88.7	
Lobular	1.4	2.1	
Other	9.5	9.2	
Basal phenotype	84.3	87.2	0.406

Conclusions: This is the first adjuvant trial specifically targeting triple-negative patients and the first X trial to target a specific molecular subtype. Accrual of the planned 868 patients is anticipated during 2009, with first safety and efficacy results in 2010 and 2011, respectively. The trial is sponsored by CIBOMA/GEICAM.

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Trastuzumab mediated cardiac dysfunction outside clinical trials: a single center experience in Asia

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Background: Trastuzumab is an effective drug for the treatment of HER2 positive breast cancer (BC); however, cardiac dysfunction (CDx) has been reported as a major adverse event. The purpose of our study was to investigate the trastuzumab mediated CDx in a practice setting and the treatment outcome at a single Asian center.
Methods: We retrospectively analyzed 129 HER2-overexpressing BC patients (pts) who were treated with a trastuzumab containing regimen between January 2005 and December 2007 at Seoul National University Hospital. We investigated the incidence of CDx and the degree of reversibility using echocardiography (EchoCG) and attempted to identify the risk factors to predict CDx.
Results: In 129 consecutive pts (median age 47; range 25−79), median left ventricular ejection fraction (LVEF) was 59% (range 45−70) measured by EchoCG. Ninety (69%) were palliatively treated and 98 (76%) had previously received anthracycline-based chemotherapy. Median duration of follow-up was 21 months. LVEF decreased more than 10% points in 10 out of 129 (7%). According to the National Cancer Institute Common Terminology Criteria for Adverse Events: left ventricular systolic dysfunction, grade (G) 2 and G 3/4 CDx developed in 4 (3%) and 8 (6%) pts, respectively. Seven (18%) pts experienced symptomatic heart failure (HF). Five pts including 3 with symptomatic HF discontinued trastuzumab, and 3 resumed trastuzumab after median 144 days (95% confidence interval; 127–162) of discontinuation. Median LVEF was 54% (range 45−63) at baseline in pts with symptomatic HF and decreased to 49% (range 33−50) after median 175 days (range 65–415) of trastuzumab treatment. HF treatment was initiated in 9 pts including 6 with symptomatic HF. Four pts received angiotensin converting enzyme inhibitors (ACEI), 3 angiotensin receptor blockers (ARB) and 2 ACEI or ARB with diuretics. The incidence of symptomatic HF was associated with lower baseline LVEF ($\leqslant$55%, p = 0.014). Though higher anthracycline cumulative dose ($\geqslant$200 mg/m^2) was noted with higher occurrence of symptomatic HF, it was not statistically significant. In the pts with symptomatic HF, LVEF was restored to 53% (range 42−59) which was similar to baseline at median 168 days (range 56–406) after the diagnosis of CDx.
Conclusions: The majority of pts with trastuzumab-associated CDx were asymptomatic and CDx was reversible.

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The prognostic importance of various clinical, pathological, and immunohistochemical parameters in tamoxifen-treated patients with early breast cancer

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Introduction: Adjuvant tamoxifen reduces the annual odds of death for women with early breast cancer by approximately 15% over 10−15 years. Since some patients experience disease progression during or after treatment with tamoxifen, it is important to identify factors that predict poor outcome and according to reduce mortality by adding chemotherapy. The primary objective of this study was to assess the prognostic importance of various clinical, pathological, and immunohistochemical parameters in tamoxifen-treated patients with early-breast cancer.
Patients and Methods: A single-institution, retrospective clinicopathological study on patients with early-breast cancer diagnosed during the years 1993–1998 that were treated with adjuvant tamoxifen. The following parameters were studied: Age, menopausal status, tumor size and location, lymph node status, pathologic grade, and immunohistochemistry for estrogen and progesterone receptors, Ki67, E-cadherin and cathepsin-D. Progression-free-survival (PFS) and overall-survival (OS) were calculated with the use of Cox-proportional hazard (CPHM), and logistic-regression (LRM) models.
Results: 211 patients with histological diagnosis of estrogen receptor-positive, invasive-breast cancer treated with adjuvant-tamoxifen were included. Median age 57 yrs (range 29−89 yrs); menopausal status – pre – 36 (17%), peri – 15 (7.1%), post – 160 (76%); node-positive – 83 (40%); progesterone receptor-positive – 120 (80%); low-grade – 33 (20%), intermediate-grade – 79 (49%), high-grade – 48 (31%); Her2/neu-positive – 19 (9%); adjuvant/neoadjuvant chemotherapy – 101 (48%), adjuvant