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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

radiotherapy – 152 (73%); disease status – AWOD – 164 (82%), DWD – 31 (15%), AWD – 6 (3%).
The only statistically-significant prognostic parameters for OS on CPHM were tumor size ($p < 0.001$), lymph-node-status ($p < 0.001$), location ($p < 0.001$), and grade ($p = 0.007$), and for PFS were tumor size ($p < 0.001$), location ($p = 0.01$), and lymph-node-status ($p = 0.03$). The only statistically-significant prognostic parameters for OS on LGM were menopausal status ($p < 0.001$), grade ($p < 0.001$), and progesterone-receptor status ($p < 0.001$), and for PFS was tumor size ($p < 0.001$).
Conclusions: This retrospective, single-institution experience validates: a) the prognostic importance of classic clinicopathological parameters including the stats of menopause, tumor size and location, lymph-node, grade and progesterone-receptor, and b) The limited prognostic value of various immunohistochemical parameters commonly-used in practice.

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The influence of polymorphism in TYMS, MTHFR and GSTP1 genes on toxicity and response in breast cancer patients treated with adjuvant chemotherapy

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Background: Genetic polymorphism in drug-metabolising enzymes and drug targets are known to be responsible for inter-individual differences in cancer treatment response and toxicity of various types of chemotherapeutics. *TYMS* and *MTHFR* variants may affect 5-fluorouracil (5-FU), capecitabine and methotrexate metabolism, while *GSTP1* influences detoxification of cyclophosphamide, doxorubicin, etoposide and platinum compounds. In the present study, 28-bp tandem repeat in *TYMS* promoter (TSER), *MTHFR* Ala222Val and *GSTP1* Ile105Val polymorphisms were investigated in relation to adverse effects in 135 breast cancer patients receiving neoadjuvant (4−9 cycles) and adjuvant (4−6 cycles) chemotherapy based on 5-FU, i.e. CAF, CMF, (n = 100) or AC, AT, TAC (n = 35) regimens.
Material and Methods: There were 135 women (mean age: 54 years, range 27−78) diagnosed with breast cancer stage I-IV included in the study. Ductal carcinoma accounted for the most frequent type of cancer (65%). Physical examination and full blood count were performed before each chemotherapy cycle. Toxicity was recorded according to the WHO criteria, after each cycle. The assessment of response concerned patients receiving neoadjuvant chemotherapy. It was based on physical examination, magnetic resonance and histopatological examination of tumor and lymph nodes of axilla. DNA was isolated from peripheral blood and the genotypes were identified using standard PCR-RFLP assay.
Results: Overall toxicity grade 3−4 was observed in 20% of patients. There were more *TYMS* 3R/3R carriers among cases with overall toxicity grade higher than 2 in all group ($P = 0.016$) and in patients receiving 5-FU-based therapy ($P = 0.047$). Also hematotoxicity grade 2−4 was noticed more often among 3R/3R homozygotes ($P = 0.076$). When gastrointestinal toxicity has been considered, grade > 2 was observed exclusively in *GSTP1* Ile/Ile or Ile/Val carriers in 5-FU treated subgroup ($P = 0.020$). Nausea and vomiting grade 2−3 were also associated with *GSTP1* Ile allele ($P = 0.058$). Response rate (complete or partial) in the group was 42%. There was slight preponderance of *TYMS* 3R/3R homozygotes and heterozygotes among responders *versus* nonresponders ($P = 0.077$). In treated with 5-FU in turn, 2R allele was found to be prevalent among good responders ($P = 0.051$).
Conclusions: Our preliminary results show that polymorphisms in *TYMS* and *GSTP1* may serve as useful predictors of toxicity and efficacy of chemotherapy in breast cancer patients, however large-scale, prospective studies are warranted.

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Triple-negative high grade invasive ductal breast carcinomas are biologically heterogeneous: differences between the basal and non-basal subtypes

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Background: Triple-negative breast carcinomas (TNBC) are characterized by their unique molecular profile, aggressive behavior, distinct patterns of metastasis, and lack of targeted therapies. Although not synonymous, the majority of triple-negative breast cancers carry the “basal-like” molecular profile on gene expression arrays. Our objective was to explore the clinicopathological characteristics of TNBC.
Material and Methods: We selected 31 consecutive cases of invasive ductal carcinomas, histological grade 3, negative for estrogen and progesterone receptors (ER/PR) and HER2 protein. We examined differences between the basal subtype determined by expression of basal cytokeratins and/or epidermal growth factor receptor, and the non-basal phenotype in relation to age, tumor size, axilla involvement, presence of lymphvascular embolization and immunoexpression of p-cadherin and p53.
Results: The results are summarized in table 1.

Table 1: Differences between the basal and non-basal subtypes of triple negative breast carcinomas of histological grade 3

subtype	n	Age range (median)	Tumor size range (median)	LVE positive (%)	Axilla positive (%)	p-cadherin (%)	p53
basal	23	30−94 y (46)	2−16 cm (4.0 cm)	8 (34.8%)	12/18 (66.7%)	4 (17.4%)	16 (69.5%)
Non-basal	8	43−66 y (51)	2−10 cm (5.3 cm)	1 (12.5%)	4/7 (57.1%)	2 (25%)	5 (62.5%)

LVE = lymphvascular embolization.

Conclusions: TNBC of the basal subtype occur in younger patients and show more aggressive pathological characteristics compared to non-basal subtype, confirming the heterogeneity of the group.

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Time-dependence of hazard ratios for prognostic factors in patients with early breast cancer

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Background: After surgical treatment of early breast cancer a life long risk for relapse persists. Hazard ratios for relapse can change during the follow-up period. The aim of our study was to study time-dependence for classical prognostic factors for relapse (age, tumor stage and grade, histological type, estrogen receptors, lymphovascular invasion (LVI) and of axillary lymph nodes involvement).
Materials and Methods: In 1035 patients with early breast cancer treated between 1983−87 at the Institute of Oncology Ljubljana (median follow-up was 17 years) we retrospectively analysed prognostic factors for relapse with Cox proportional hazard model and with test for violation of proportional hazard assumption (method of Schoenfeld’s residuals).
Results: Tumor size, grade and estrogen receptors (ER) were time-dependent prognostic factors for breast cancer relapse. Tumor size >2 vs. $\leqslant$2 cm (HR 1.59; 95% CI 1.21−2.10) and grade G2/3 vs. G1 (HR 2.08; 95% CI 1.39−3.13) were unfavorable prognostic factors in the first five years after surgery and lost their prognostic role thereafter. Positive ER (ER+ vs. ER) were a favorable prognostic factor only in the first year after surgery, from 1−5 years they had no prognostic role, after 5 years they became borderline unfavorable prognostic factor (HR 1.50 95% CI 0.98−2.30). Positive axillary lymph nodes (4−9 lymph nodes: HR 2.55; 95% CI 1.91−3.40; $\geqslant$10 lymph nodes: HR 4.65; 95% CI 3.29−6.58) and LVI (HR 1.58; 95% CI 1.21−2.06) were time-independent risk factors throughout the follow-up.
Conclusions: Tumor stage and grade are time-dependent unfavorable prognostic factors, being significant only in the first 5 years after surgery. Positive ER changes their prognostic role with time, from being shortly favorable to being unfavorable. More then 3 involved axillary lymph nodes and LVI are time-independent unfavorable prognostic factors throughout the follow-up period.

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A tool to improve personalized cancer care: measuring the response of circulating epithelial tumour cells (CETC) and tumour stem cell subpopulations to therapy in the individual patient

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Background: Cells released from the primary tumour persisting and recirculating in the host can lead to the formation of distant metastases. We can show that CETC are detectable and can be quantified in the peripheral blood of almost all cancer patients including early-stage solid malignancies, although it was claimed that such cells are detectable only in a minor fraction of early-stage cancer patients.
Material and Methods: Using anticoagulated peripheral blood and red blood cell lysis as the only enrichment step, one centrifugation step, staining live cells with fluorochrome labelled anti-epithelial antigen as a search antibody, automated image analysis for detection of positive events