were delivered. In arm A, 16.7% of the patients had one or more cycles delayed due to side effects, compared with 19% in arm B and 2.5% in arm C. 23.8% of the patients in arm A experienced a grade 3 infection or febrile neutropenia compared to 4.7% and 15% in the B and C arm respectively, a retrospective calculation of events in relation to possible events (cycles) resulted in 3.6% (arm A), 0.6% (arm B) and 3.1% (arm C) events per cycle.

An amendment (an extra week between the EC and T parts) was introduced after 124 cycles in the A and B arm due to six grade 3 hand-foot-skin reactions during the docetaxel part. After the amendment, one grade 3 event occurred in the EC and T arm, respectively, in 496 cycles. In the A and B arm, 28.6% (12 in each arm) of the patients were hospitalized due to side effects and the corresponding figure in the C arm was 20% (8 patients).

Conclusion: The concept of dose-dense and tailored EC/T is manageable and is presently studied in a randomized phase III study together with the Austrian Breast and Colorectal Study Group (SBG 2004−1/ABCSG-25).

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Safety data from a phase II study of neoadjuvant bevacizumab and trastuzumab administered with albumin bound paclitaxel (nab paclitaxel) and carboplatin in HER2+ locally advanced breast cancer

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Background: SPARC is a known prognostic factor for poor survival and its expression has been shown to increase with tumor aggressiveness. Preclinical evidence suggest that SPARC may mediate enhanced intratumoral accumulation of albumin-bound paclitaxel (Abraxane®, *nab*-paclitaxel) through its interaction with albumin. In a prior phase III study of patients with metastatic breast cancer, *nab*-paclitaxel resulted in higher response rate and an increased time to progression compared with standard solvent-based paclitaxel. The addition of biologic targeted therapies added to standard chemotherapy in breast cancer has translated into improved outcomes. This multicenter phase II pilot study was designed to evaluate the feasibility, toxicity, and preliminary efficacy of dual VEGF and HER2 monoclonal antibody receptor blockade with bevacizumab (B) and trastuzumab (T) administered in combination with neoadjuvant *nab*-paclitaxel and carboplatin.

Methods: Eligibility: cT1−4, N0−3, M0 adenocarcinoma (T1N0M0 excluded), FISH HER2+, normal LVEF, ECOG PS $\leqslant$ 2, adequate organ function, controlled hypertension (HTN), neuropathy $\leqslant$ grade 1, tumor tissue availability for SPARC testing. Treatment: Nab-paclitaxel 100 mg/m^2 days 1, 8, 15 q28 days with carboplatin AUC of 6 day 1 q28 days $\times$ 6 cycles, B 5 mg/kg qwk $\times$ 23 wks with T 4 mg/kg loading dose followed by 2 mg/kg qwk $\times$ 22 wks. Surgery $\geqslant$4 wks following last B. T at 6 mg/kg and B 15 mg/kg q3wk post op for a total of 1 year (B reinitiated $\geqslant$4 weeks post op). LVEF measurements at baseline, 3, 6, 12, and 18 months. SPARC immunohistochemistry assessments were performed and scored on a 0−3 level (0 = absent, 1 = weak, 2 = moderate, 3 = strong).

Results: 25 pts are evaluable for toxicity. Histology: ductal 80%, lobular 12%. 48% ER and PR negative, ECOG PS 0 – 90%. Grade 3/4 hematological toxicity in >5% of patients consisted only of neutropenia in 12 pts (48%). Nonhematologic toxicity was only notable for grade 3 hypertension in 3 pts (13%). No LVEF dysfunction was noted. 4 pts went off study: 2 − pt wishes, 2 – toxicity (fatigue, reflux). 2 pts did not complete post operative maintenance therapy (unrelated to treatment).

Conclusion: Neoadjuvant dual monoclonal antibody receptor blockade with bevacizumab plus trastuzumab in combination with *nab*-paclitaxel and carboplatin is feasible. No unexpected toxicities and no early evidence of LVEF dysfunction have been reported. SPARC tumor assessments are ongoing and will be presented.

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Concurrent or sequential adjuvant hormonoradiotherapy after conservative surgery for early-stage breast cancer: first results of the CO-HO-RT phase II randomized trial

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Background: We recently showed in an aromatase-gene transfected breast cancer cell line, a radiosensitizing effect of letrozole. We then conducted a multicentric phase II randomized trial evaluating adjuvant concomitant radiotherapy and letrozole with radiotherapy followed by letrozole in postmenopausal early breast-cancer patients (CO-HO-RT trial).

Methods: Postmenopausal pts with early-stage breast cancer were randomized after conservative surgery to either: A) concurrent RT-LET (LET started 3 weeks before the first day of RT) or B) sequential RT-LET (LET started 3 weeks after the end of RT). Whole breast RT was delivered to a total dose of 50 Gy +/− a 10−16 Gy boost. Pts were stratified by center, adjuvant chemotherapy (ACT), boost, CD8 radiation-induced apoptosis. Primary endpoint was radiation-induced acute and late skin toxicity. Skin toxicities were evaluated by two different clinicians at each medical visit (CTCAE v3.0). Lung CT-scan and functional pulmonary tests were performed regularly. Quality of life and cosmetic assessments were registered. DNA samples were screened for SNPs in the ATM genes.

Results: A total of 150 pts were randomized between 01/05 and 02/07. Median follow-up was 17 months (range, 6−49). No statistical differences were identified between the two arms in terms of mean age; initial TNM; median surgical bed volume; post surgical breast volume. ACT and RT boost were delivered in 19% and 38% of pts, respectively. Overall, 10 patients (6.7%) presented grade 3 acute skin dermatitis during RT without differences between both arms. Grade 2 acute skin dermatitis were observed in 36.5% and 32% in arm A and B, respectively but symptoms rapidly settled in most patients by months 3, 6, and 12. Grade 2 radiation-induced subcutaneous fibrosis were found in 8 patients (5%) with a slight difference in disfavor of arm B (7%) vs 4% in arm A. Three patients (2%) presented a grade 2 pneumonitis (all in arm A). Overall, quality of life and cosmesis were good to excellent.

Conclusions: Concurrent or sequential adjuvant radiohormonotherapy with letrozole is feasible in daily practice. Identifying hypersensitive patients with CD8 RIA or ATM screening will help tailoring treatments.

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Relationship between estrogen receptor (ER) status and efficacy of postoperative adjuvant chemotherapy with oral tegafur-uracil (UFT) or CMF: subset analysis from a randomized controlled trial (CUBC trial in Japan)

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Background: It has been reported that UFT decreased the risk of relapse by 21% in patients with Stage I to III breast cancer and risk of mortality by 35% in patients with node-negative breast cancer (Kasumi *et al*., Oncology 2003; Noguchi *et al*., J Clin Oncol 2005). We previously reported three-year follow-up data from a randomized comparative study comparing classical CMF (6 courses) plus tamoxifen (TAM) with UFT (2 years) plus TAM in patients with operable node-positive breast cancer (Inaji *et al*., ASCO 2004). We now report a five-year follow-up data and the relationship between estrogen receptor (ER) status and the efficacy in each treatment group.

Materials and Methods: A total of 350 patients, 173 patients in the CMF + TAM group [CPA 65 mg/m^2 (po): days 1 to 14, MTX 40 mg/m^2 (iv):

days 1 and 8, 5-FU 500 mg/m^2 (iv): days 1 and 8, plus TAM 20 mg/day (po) for 2 years] and 177 patients in the UFT + TAM group [UFT 270 mg/m^2/day (po) plus TAM 20 mg/day (po), both given for 2 years], were included in a subset analysis of relapse-free survival (RFS) based on ER status, a stratifying factor for randomization.

Results: Five-year overall RFS was 76.3% and 72.3% in the CMF and UFT groups, respectively, showing no significant difference between the two groups (Hazard ratio (HR): 1.18 (0.76−1.79), p = 0.456). In ER(−) patients, RFS was 74.7% and 61.4% in the CMF (n = 73) and UFT (n = 72) groups, respectively (HR: 1.63 (0.90−3.02)). In ER(+) patients, RFS was 75.7% and 80.8% in the CMF (n = 89) and UFT (n = 91) groups, respectively (HR: 0.72 (0.37−1.38)). An interaction was observed between ER status and the efficacy in each group (test for interaction: p = 0.07). RFS was not significantly different between ER(−) and ER(+) in the CMF group (p = 0.79), but was markedly different between ER(−) and ER(+) in the UFT group (p = 0.002).

Conclusions: UFT may be very promising in preventing relapse of ER(+) breast cancer. While there have been many reports that postoperative chemotherapy is not very effective for ER(+) breast cancer, tegafur-based oral chemotherapy such as UFT and S-1 (tegafur, CDHP, Oxo) are expected to be effective preoperative chemotherapy for ER(+) breast cancer, if used in combination with endocrine therapy. This possibility needs to be investigated in a future study.

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Letrozole or anastrozole for the prevention of early recurrences in post menopausal women with early stage breast cancer: using number needed to treat (NNT) to compare benefit

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Background: The ATAC (Lancet, 2005) and BIG 1-98 (NEJM, 2005) randomized trials demonstrated that anastrozole and letrozole were more effective than tamoxifen in preventing disease relapse in postmenopausal women with early stage breast cancer. However, recent secondary analyses of these trials revealed important differences between letrozole and anastrozole in the prevention of early distant recurrences; early being defined as less than three years following the initiation of treatment. NNT represents the number of patients that need to be treated with a new intervention in order to avoid one additional event, and is a powerful approach that can be used to make sense of numerical results from clinical trials. In this exploratory analysis, the NNT approach was used to compare letrozole and anastrozole in preventing early recurrences in this patient population.

Methods: The early recurrence data from the pivotal trials for letrozole and anastrozole were reviewed (Mauriac, 2007, Houghton, 2006). A key requirement for a NNT analysis is that all outcomes must be considered over similar time periods. The time points for evaluating early recurrences for anastrozole and letrozole were at 2.5 and 2 years respectively. Patients remaining disease free beyond these time points were censored. NNT, which is the reciprocal of the percent difference in efficacy relative to tamoxifen was calculated for each agent with respect to all recurrences; local-regional, distant recurrences and contralateral breast cancer.

Results: For all recurrences, letrozole and anastrozole had a comparable NNT of 75 (95% CI: 46–200) and 77 (95% CI: 39–2349) patients to avoid one recurrence. However, a 3-fold difference in NNT was noted for distant recurrences in favor of letrozole; 100 (95% CI: 58–371) patients would have to be treated with letrozole to avoid one such event compared to 300 (95% CI: 74−∞) with anastrozole.

Discussion: In situations of multiple numerical outcomes from randomized trials, the NNT approach is a simple and effective method to express the findings in a clinically meaningful way. In this analysis, it appears most of the clinical benefit associated with anastrozole in the first 2−3 years is in reducing the risk of local and regional relapses, while letrozole shows a pronounced impact in reducing distant metastases in these first 2−3 years. These findings are particularly relevant because distant metastases are associated with the lowest survival rates and represent a major economic burden to health care systems.

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Taxane-containing primary chemotherapy for inflammatory breast cancer: INT experience

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Background: The effect of taxanes on the survival of patients with IBC (inflammatory breast cancer) has not been established since these patients generally represent a subset of global primary chemotherapy or phase II trials.

Material and Methods: We analyzed the medical records of 93 women consecutively treated at the Istituto Nazionale Tumori in Milan from October 1992 to August 2007 with an integrated program of primary ± adjuvant chemotherapy, surgery, radiotherapy and endocrine therapy and/or trastuzumab if indicated.

Results: From October 1992 to November 1994, 13 patients were treated with primary single agent anthracycline (A) followed by postoperative CMF. Subsequently, till August 2007, 80 patients were given primary chemotherapy containing both anthracyclines and taxanes (AT). Main pretreatment characteristics were fairly well distributed between the two case series. Treatment outcome in terms of clinical complete remission (cCR), disease progression while on primary chemotherapy (PD), absence of invasive breast cancer (pCR) and absence of involved axillary nodes (pN0), freedom from progression (FFP) and overall survival (OS) at 5 years is reported in the table.

	% cCR	% PD	% pCR	% pN0	% FFP	% OS
A	8	0	8	0	12±10	44±10
AT	34	2.5	20	36	45±6	62±6
				P = 0.005	P = 0.20	

Multivariate analysis on FFP revealed pN0 as the strongest indicator of prognosis (HR 3.5, P = 0.006). However pCR (HR 2.8, P = 0.09) and AT regimen (HR 1.8, P = 0.10) also played an important role. In the AT series the only variable able to significantly predict the achievement of pathological complete remission in both breast and axilla was the status of PgR (negative v. positive, odds ratio 1.5, P = 0.03), which however failed to reach conventional statistical significance in the multivariate analysis (P = 0.17).

Conclusions: The retrospective analysis shows that the use of AT-containing regimes is associated with higher likelihood of pCR and pN0, which represent the factors more strongly associated with a favorable long term outcome.

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The SUCCESS-Trial – toxicity analysis of a phase III study evaluating the role of Docetaxel and Gemcitabine in the adjuvant therapy of breast cancer patients

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Background: In several randomized trials, taxane containing regimens have demonstrated superiority compared to mere anthracycline containing schedules for the adjuvant treatment of patients with early breast cancer. Given an array of novel drugs, continued improvements in the adjuvant setting may further reduce breast cancer mortality in future.

Methods: The SUCCESS-Study is an open-label randomized controlled, Phase III study comparing the disease free survival after randomisation in patients treated with 3 cycles of Epirubicin(100 mg/m^2)–Fluorouracil(500)–Cyclophosphamide(500) (FEC)-chemotherapy, followed by 3 cycles of Docetaxel(100 mg/mg^2) (D) versus 3 cycles of FEC, followed by 3 cycles of Gemcitabine(1,000 mg/m^2 d1, 8)–Docetaxel(75 mg/m^2) (DG). Complete, monitored toxicity data of 2.691 pts were available for this analysis.