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.

Results: Cytostatic treatment was prematurely stopped in 119 pts (4.4%) receiving FEC-DG and in 103 pts (3.8%) with FEC-D (p = 0.21). Dose reduction >20% (3.97% vs 2.90%) and postponement of treatment cycles >7die (22.85% vs 14.19%) was rare, but more frequent in the FEC-DG arm (both p < 0.001). G-CSF support was applied in 850 (29.2%) vs. 602 pts (20.7%, p < 0.001). Toxicities NCI grade >2 which occurred with incidence >1% or significantly different in the two arms are depicted in Table 1. Afebrile and febrile neutropenia and anemia did not differ between the two arms, but thrombocytopenia was more frequent in FEC-DG (1.7%, p = 0.007). Hand-foot syndrome and neuropathy was more frequent in the FEC-D arm (p = 0.09 and p = 0.02, respectively).

Conclusion: Severe adverse effects were rare in both treatment arms. The addition of gemcitabine to FEC-D adjuvant chemotherapy increases toxicity moderately. These findings will have to be interpreted in the context of survival outcome results.

Table 1

Toxicity	Grade >2		Percentage		p-value
	FEC-DG	FEC-D	FEC-DG	FEC-D	
Neutropenia	504	508	0.3490	0.3458	0.9984
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0×10^9/L, fever ⩾38.5ºC)	42	59	0.0291	0.0402	0.4454
Anemia	31	20	0.0215	0.0136	0.4556
Thrombocytopenia	25	6	0.0173	0.0041	0.0070
SGPT (ALT) (serum glutamic pyruvic transaminase) elevation	68	28	0.0471	0.0191	0.0004
GGT (Gamma-Glutamyl transpeptidase)	45	34	0.0312	0.0231	0.6205
Vomiting	55	58	0.0381	0.0395	0.9981
Nausea	43	45	0.0298	0.0306	0.9994
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	24	26	0.0166	0.0177	0.9971
Diarrhea patients without colostomy	41	39	0.0284	0.0265	0.9927
Fatigue (lethargy, malaise, asthenia)	40	46	0.0277	0.0313	0.9539
Bone pain	28	44	0.0194	0.0300	0.3381
Thrombosis/embolism	28	22	0.0194	0.0150	0.8396
Arthralgia (joint pain)	24	29	0.0166	0.0197	0.9409
Headache	21	10	0.0145	0.0068	0.2469
Myalgia	20	37	0.0139	0.0252	0.1809
Dyspnea	19	24	0.0132	0.0163	0.9175
Hand-foot skin reaction	15	33	0.0104	0.0225	0.0876
Neuropathy	9	28	0.0062	0.0191	0.0227

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Economic assessment of late extended adjuvant letrozole following a prolonged therapy break from Tamoxifen – MA-17 post-unblinding analysis

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Background: The MA17 study was a randomized double-blind placebo-controlled trial of 5 years of letrozole (LET) 2.5 mg/d in 5187 post-menopausal women (median age 62 yrs) with early breast cancer after 5 years of adjuvant tamoxifen (TAM). Due to significant improvement in disease-free survival with LET, the study was unblinded at the first interim analysis (mean follow-up 2.4 years). At this point (median time from TAM, 2.5 years), patients receiving placebo (PLAC) were offered LET. 1,655 patients accepted LET, 613 patients elected no treatment. After a median 2 year follow-up, DFS and DDFS were highly significantly improved in the PLAC-LET group after adjusting for differential demographics and disease characteristics. This analysis estimates the incremental cost per QALY gained (ICQ) of 5 years LET after the observed 2.5 year therapy break after TAM versus no extended adjuvant therapy from a national health service perspective.

Methods: A Markov model described the natural history of breast cancer via contralateral tumour, locoregional, and distant recurrence, also accounting for the effects of osteoporosis. Annual contralateral, recurrence and osteoporosis rates were obtained from the PLAC arm of the post-unblinding analysis, to which the adjusted HRs for the PLAC-LET group were applied. Effects of osteoporosis and recurrent events, and health state utilities were informed by published studies. Costs (2006 £) of breast-cancer care were obtained from a primary costing study in 2006. A probabilistic sensitivity analysis was undertaken, and all outcomes were discounted at 3.5% annually.

Results: The results show that the PLAC-LET group gain 14.14 QALYs compared to 13.84 in the PLAC group, lifetime costs £8,477 and £4,524, respectively. The mean incremental cost per QALY is £13,154. The probabilistic sensitivity analysis estimates a 95% credible interval of £9,153–27,094, with an 87% probability of cost-effectiveness at a £20,000 value of a QALY.

Conclusions: Late extended adjuvant Letrozole therapy after a prolonged therapy break from Tamoxifen (1−5 years) is a cost-effective use of health care resources.

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99mTc-MIBI elimination by a tumor and response to chemotherapy in locally advanced breast cancer patients

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Aim: To estimate predictive significance of 99mTc-MIBI accumulation and elimination by tumor on the effectiveness of neoadjuvant chemotherapy in locally advanced breast cancer patients.

Materials and Methods: Investigation of accumulation and elimination of 99mTc-MIBI by tumor was performed in 45 breast cancer patients (stages: IIa − 1, IIb − 1, IIIa − 7, IIIb − 31, IIIc − 5 patients) before the beginning of chemotherapy (CAF, FAC, docetaxel, 3−6 cycles). 99mTc-MIBI was introduced intravenously (555 MBq), with the following two-phase (in 15 min and in average 3 hours) static scintigraphy of a breast. Coefficient of relative accumulation (CRA) of 99mTc-MIBI in tumors in 15 min after injection (CRA1), CRA after 3 hours (CRA2), and percent of elimination (PE) were calculated [PE = (CRA1 − CRA2)×100/CRA1]. All patients were operated. “No residual tumor” and “Microscopic residual tumor” were united as “pathological effect”.

Results: Clinical effect was observed in 82% (complete effect in 6, partial effect in 31, stabilization in 7, and progression in 1 patient). Pathological effect was observed in 29% (no residual tumor in 4, and microscopic residual tumor in 9 cases). The levels of CRA1 and CRA2 did not influence on the frequency of clinical or pathological effects. In patients with high level of the PE pathological effect was not attained (see table). High level of the PE was reviewed more rarely (2p < 0.05) in patients with ER− HER2neu− tumors (19%), than in patients with ER+ HER2neu− tumors (47%), and than in patients with HER2neu+ tumors (75%).

Table. PE level and frequency of clinical and pathological effects

PE level	Frequency of clinical effects	Frequency of pathological effects
Low (<21%)	87% (26/30)	43%* (13/30)
High (>22%)	73% (11/15)	0%* (0/15)

*- 2p < 0.05.

Conclusion: Our first results confirm the main hypothesis: rapid 99mTc-MIBI elimination by a tumor predicts the low pathological response to chemotherapy. Detection of the high level of 99mTc-MIBI PE by tumor can indicate that neoadjuvant target therapy may be more preferential, than chemotherapy.

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Safety and feasibility of biweekly neoadjuvant gemcitabine, epirubicin, and albumin bound nab-paclitaxel (GEA) in locally advanced breast cancer – results of a phase II study

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Background: The triplet combination of gemcitabine (G), anthracyclines and taxanes have demonstrated significant activity as neoadjuvant therapy. Nab-paclitaxel is a novel albumin-bound form of paclitaxel that allows for the preferential delivery of paclitaxel to the site of the tumor via gp60/caveolin-1 transcytosis and the albumin binding protein SPARC. In preclinical models as well as in a phase III metastatic breast cancer trial, single agent nab-pacltiaxel was shown to increase both response rate and TTP compared with standard solvent based paclitaxel. In this multicenter phase II study, the