Results: 153 women were surveyed with a median age of 60. 51% had node-negative disease, 89% had prior radiation, 61% had prior chemotherapy and 59% had prior tamoxifen therapy. The mean duration of AI therapy was 31 months. 30% of women required a 5-year survival benefit of less than 1% and 27.5% needed a decrease in recurrence risk of less than 1% to continue an AI beyond 5 years. In contrast, none of the 40 MOs surveyed felt a survival benefit or decrease in recurrence risk of less than 1% was sufficient to prescribe an AI for an additional 5 years. There was a significant correlation between increased severity of menopausal/endocrine symptoms experienced on AIs and an increased minimum survival benefit required for women to continue therapy ($p = 0.036$).

Conclusions: While approximately one-third of patients are willing to continue AIs for a benefit of less than 1%, no physician surveyed is willing to prescribe an AI beyond 5 years for this benefit. Patients' willingness to continue AIs beyond 5 years correlates to the severity of the side effects they experienced while on AIs.

Patient & physician opinion of minimum benefit required to continue AIs beyond 5 years

	<1%	1–2%	2–5%	5–10%	10–15%	15–20%	>20%	Unknown
Patient opinion:								
Survival benefit	46 (30.1%)	22 (14.4%)	18 (11.8%)	19 (12.4%)	6 (3.9%)	6 (3.9%)	26 (17.0%)	10 (6.5%)
Decrease in recurrence	42 (27.5%)	22 (14.4%)	20 (13.1%)	22 (14.4%)	7 (4.6%)	9 (5.9%)	22 (14.4%)	9 (5.9%)
Physician opinion:								
Survival benefit	0 (0.0%)	18 (45.0%)	15 (37.5%)	5 (12.5%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	1 (2.5%)
Decrease in recurrence	0 (0.0%)	1 (2.5%)	15 (37.5%)	14 (35.0%)	5 (12.5%)	0 (0.0%)	1 (2.5%)	4 (10.0%)

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Defining a numerical threshold for chemotherapy using Adjuvantonline

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Background: Adjuvantonline (Aol) is a decision support tool used by oncologists to compute the absolute benefit from adjuvant therapies including chemotherapy. It allows individualised discussion with the patient. This approach has supplanted more general consensus recommendations from the St Gallen and NIH Panels. However, both St Gallen and the NIH explicitly recognise a threshold for chemotherapy. We have found that one drawback to Aol is the absence of a clear threshold to begin chemotherapy discussions. In this study, we seek to evaluate such a threshold.

Methods: We used Aol to estimate the absolute benefit from chemotherapy in a group of 295 patients whose gene expression risk profile had been previously been determined with Mammaprint. We then varied the Aol numerical threshold for a decision to treat in order to examine the effect of this threshold on the accuracy of patient selection for chemotherapy.

Results: Aol's ability to select high risk patients and exclude low risk patients from chemotherapy is comparable to (but no better than) treatment decisions based on the NIH and the St Gallen recommendations. Its accuracy improves as the threshold is increased to 3%, and then plateaus (see table).

Effect of varying Aol threshold for a chemotherapy recommendation in 295 patients previously sorted into high risk and low risk groups by gene expression profiling. (A false positive decision would give chemotherapy to a low risk patient; false negative decision would withhold chemotherapy from a high risk patient).

AOL benefit (%)	false positive (%)	false negative (%)	accuracy (%)
1	83	2	58
2	66	10	62
3	48	14	69
4	41	23	68
5	23	33	72
6	20	41	70

Conclusions: This study allows oncologists to evaluate an Adjuvantonline numerical threshold below which chemotherapy need not be discussed. We suggest that it can be used to support a "3% discuss, 5% recommend" threshold. This quantitative Adjuvantonline threshold would be broadly compatible with those that had earlier been agreed at the St Gallen and NIH Consensus conferences, would standardise chemotherapy use between different breast units, and would allow patients to be spared the distress of an unnecessary chemotherapy discussion.

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Breast conservation and long term survival after neo-adjuvant chemotherapy

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From 01.1985 to 04.1998, a randomised trial was conducted to compare first line mastectomy followed with adjuvant medical treatment (n = 138) to neo-adjuvant chemotherapy followed with adjusted loco-regional treatment (n = 134) for women with too big tumours to be treated with immediate conserving surgery.

After total mastectomy, patients received adjuvant chemotherapy (n = 110) in case of histological nodal involvement (n = 82) or absence of oestrogen and progesterone receptor (n = 28). Patients without these poor prognostic factors (n = 28) did not received adjuvant medical treatment. No irradiation was delivered in this group.

After neo-adjuvant treatment 63% of patients had conserving treatment: 33% had exclusive irradiation thanks to clinical complete response and 30% had conserving surgery followed with breast irradiation in case of residual tumour smaller than 2 cm. Remaining patients (37%) were treated with total mastectomy without irradiation because of residual tumour bigger than 2 cm.

With a 20 year median follow-up, overall survival and distant disease free survival are identical between the two groups, being both 55% at 15 year respectively.

As a stratification was done before randomisation between positive and negative steroid receptor, we can analyse distant disease free survival in these 2 subgroups: there is no difference between neo-adjuvant chemotherapy and first line mastectomy. But EPR negative tumours have earlier recurrences than positive tumours, whereas positive tumours have more frequently late recurrences.

Patients treated with neo-adjuvant chemotherapy had more often local recurrences (breast, chest wall, axillary or internal mammary nodes), due to exclusive irradiation given in case of clinical complete response. Nevertheless, in this subgroup of non-operated women, recurrences were more often localized in axilla (n = 10) than in breast (n = 4). Finally with this very long follow-up, one out of 4 breast-sparing patients had secondary salvage mastectomy because of local recurrence. A large majority of these local recurrences (80%) occurred within the first 5 years.

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A randomized feasibility/phase II study (SBG 2004-1) with dose-dense/tailored epirubicin, cyclophoshamide (EC) followed by docetaxel (T) or fixed dosed dose-dense EC/T versus T, doxorubicin and C (TAC) in node-positive breast cancer

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Background: The primary aim of the study was to evaluate the toxicity and feasibility of a both tailored (possibility of dose escalation) and dose-dense (biweekly) EC/T and of the same regimen given with fixed doses as adjuvant breast cancer therapy. The TAC regimen served as a standard arm.

Patients and Methods: Patients with node-positive breast cancer were randomized to either four cycles of biweekly and tailored EC (dose range: epirubicin 38–90–120 mg/m^2, cyclophosphamide 450–600–1200 mg/m^2) followed by four cycles of docetaxel (60–75–90 mg/m^2) (arm A) or to the same regimen with fixed doses (E90C600 x 4 $\rightarrow$ T75 x 4) (arm B) or to docetaxel, adriamycin and cyclophosphamide (T75A50C500 x 6) every third week (arm C). All regimens were given with G-CSF support and prophylactic ciprofloxacin. The toxicity was evaluated according to NCI, CTC, version 3.0.

Results: Between November 2005 and May 2006 124 patients were randomized. A total of 305 (arm A), 315 (arm B) and 222 (arm C) cycles

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):