Methods: BM aspirates from 275 primary breast cancer patients were included into the study. A double immunofluorescence staining procedure was established for the identification of cytokeratin-positive (CK)/ERα positive cells. ERα status of the primary tumor was immunohistochemically assessed using the same antibody against ERα.

Results: In 113 of 275 (41%) breast cancer patients CK-positive cells could be detected in BM. The number of detected cells ranged between 1 and 55 cells per 2×10^6 mononuclear cells. Disseminated tumor cells demonstrated ERα positivity in 15 (13%) of these 113 patients. The ERα expression on DTC was heterogeneous in 12 of 15 (80%) patients. Concordance rate of ERα status between primary tumor and DTC was 26%. Only 13 of 94 patients with ER α positive tumors had also ERα positive DTC.

Conclusions:

1. The hormone receptor status between primary tumor and corresponding DTC may differ.
2. This discrepancy may explain the rate of non-responders to adjuvant endocrine therapy despite ER-positive primary tumor.
3. These patients may benefit from adjuvant therapy regimens based on antibody strategies or bisphosphonates.

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NEWEST: a Phase II, randomised, neoadjuvant trial comparing fulvestrant 500 mg vs 250 mg in postmenopausal women with locally advanced, oestrogen receptor-positive (ER+) breast cancer

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Background: Fulvestrant (Faslodex®) is a selective ER antagonist with a distinct mode of action used in the treatment of postmenopausal women with advanced breast cancer. Two pre-surgical studies showed dose-related reductions in ER expression and Ki67 labelling index (LI) with doses up to 250 mg. Here we present a comparison of the biological and clinical activities of the fulvestrant approved (AD) vs high-dose (HD) regimens.

Materials and methods: NEWEST compared fulvestrant AD (250 mg/month) vs HD (500 mg/month plus 500 mg on Day 14 of month 1) as 16 wks' neoadjuvant therapy for postmenopausal women with ER+, locally advanced breast cancer. Core biopsies were taken at baseline, Wk 4 and at surgery (Wk 16) and assessed for changes in Ki67 LI, ER and progesterone receptor expression. The primary objective was effect on Ki67 LI at Wk 4. Secondary objectives included assessment of tolerability and tumour response by 3-D ultrasound. Responses were classed as complete (disappearance of all lesions) or partial (⩾65% reduction in tumour volume) and disease progression (⩾73% increase).

Results: Overall 211 women (mean age 67 years) were included (HD: n = 109; AD: n = 102); 99% had ER+ disease. Fulvestrant HD (n = 60) reduced mean Ki67 LI to a significantly greater extent than AD (n = 63) [−78.8% vs −47.3%, p < 0.0001] at Wk 4. This was associated with a significantly greater (p < 0.0003) reduction in ER at Wk 4 for HD vs AD (ChromaVision™ Intensity Score). Similar trends in Ki67 LI and ER were observed for HD vs AD at Wk 16. At Wk 16, response rates (ITT) were 22.9% and 20.6% for HD and AD, respectively. In a post-hoc analysis of patients with a complete 16-wk assessment (n = 69 both arms), response rates were 36.2% for HD and 30.4% for AD. Seven patients receiving HD progressed during therapy vs 8 for AD. Both doses were well tolerated. Reductions in endometrial thickness were similar between HD and AD and neither affected serum bone marker levels.

Conclusions: NEWEST is the first study to compare the biological and clinical activity of fulvestrant AD and HD and provides the first clinical indication that fulvestrant HD has significantly greater activity in terms of reductions in Ki67 LI and ER expression. All other efficacy parameters were numerically in favour of the HD regimen. Both doses were well tolerated with no detrimental effects on endometrial thickness or bone markers. Fulvestrant HD is being investigated in metastatic disease in the CONFIRM trial.

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Hormone-receptor status and likelihood of predicting pathological complete response (pCR) in the NOAH trial of neoadjuvant trastuzumab in patients (pts) with HER2-positive locally advanced breast cancer (LABC)

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Background: The NOAH trial evaluated the addition of neoadjuvant trastuzumab (Herceptin®; H) to chemotherapy for pts with HER2-positive LABC. Significant improvement of pCR rates in both breast and axilla with this regimen has been reported previously (Gianni et al. ASCO 2007; abs 532).

Materials and Methods: 228 pts were randomised to receive 3 cycles of doxorubicin (60 mg/m^2) and paclitaxel (150 mg/m^2) q3w, 4 cycles of paclitaxel (175 mg/m^2 q3w) and 3 cycles of CMF (C 600 mg/m^2, M 40 mg/m^2, F 600 mg/m^2 d 1+8 q4w) with or without concomitant H (8 mg/kg loading dose then 6 mg/kg q3w for 1 year) before surgery. In parallel, 99 pts with HER2-negative breast cancer received the same chemotherapy regimen.

Results: Main pretreatment characteristics (inflammatory vs non-inflammatory breast cancer; clinical node involvement; oestrogen receptor (ER), progesterone receptor (PgR) and menopausal status; age

	Total pCR	ER negative vs positive	PgR negative vs positive
HER2 negative, no H	16%	32% vs 6% (p = 0.0007)	26% vs 6% (p = 0.007)
HER2 positive, no H	20%	22% vs 17% (p = 0.51)	23% vs 12% (p = 0.24)
HER2 positive, H	39%	48% vs 18% (p = 0.002)	48% vs 11% (p = 0.006)

No other variable significantly influenced pCR rate. The likelihood that pretreatment characteristics predicted for pCR was assessed in multivariate analyses. In the HER2-positive population, addition of H (odds ratio [OR] 2.68; 95% confidence interval [CI] 1.46, 4.93; p = 0.0015) and negative PgR status (OR 4.49; 95% CI 1.79, 11.27; p = 0.015) were the only variables predicting for pCR. In pts not given H, HER2 status did not influence treatment results but PgR status significantly predicted for pCR (OR 3.56; 95% CI 1.47, 8.95; p = 0.007).

Conclusions: PgR status was the strongest independent variable, together with H treatment, associated with pCR in HER2-positive LABC. PgR status was also the only variable associated with pCR in the 2 groups of pts who did not receive H, ie HER2-negative pts (not eligible for H) and HER2-positive pts randomised to the non-H arm. These data highlight the relevance of crosstalk between hormone and HER2 receptors in modulating response to H.

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How much benefit is needed to continue aromatase inhibitors (AIs) beyond 5 years – A patient and physician survey

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Background: AIs have been shown to improve disease-free survival in post-menopausal women with hormone receptor positive early breast cancer. Trials are ongoing to determine if AI therapy should be continued beyond 5 years. The objective of this study was to assess the minimum disease-free and overall survival benefit acceptable to physicians prescribing AIs and to women undergoing treatment with AIs to continue treatment beyond five years.

Methods: Women with stage I–III breast cancer with at least one year of adjuvant AI therapy completed a self-administered survey assessing relevant social, cancer-related, and treatment factors, and FACT-ES (version 4). The minimum benefit was denoted as percentage decrease in risk of cancer recurrence and percentage increase in survival at 5 years. Medical oncologists (MOs) treating breast cancer across Canada were also surveyed.

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