**223** Poster

**The molecular classification of breast cancer according to the stem-cell model provides important informations for systemic adjuvant treatment decision**

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**Background:** The link between the estrogen receptor (ER) and tumor growth belongs to the fundamentals of endocrine responsiveness of breast cancer. A negative association of ER expression and proliferation has been documented for normal breast but seem to differ for breast cancer subtypes descended from distinct progenitor cells. Despite the growing evidence of the stem cell concept for breast cancer there are no data in terms of therapy benefit of those tumors.

**Material and Methods:** We compared the link between ER expression and proliferation in breast cancers with stem cell like features and more mature types. Affymetrix microarray data of more than 1300 breast cancer samples were stratified using the expression of a Stem Cell Like (SCL) signature of coordinatively expressed genes containing stem and progenitor cell markers as e.g. CK5/6, CK14, ITGA6 and CD133.

**Results:** A conserved inverse link of ER and Ki67 expression as a surrogate for proliferation among SCL+ tumors (n = 357/1369 [26 %]) allowed the delineation of those ER positive tumors in the Non-SCL group where this link is uncoupled. Uncoupling was observed for about one third of all breast cancers. These tumors were characterized by a prognosis inferior to the ER negative cancers despite an apparent positive ER status with lower 5 and 10 year survival rates (HR: 2.05; 95% CI 1.61−2.61; P < 0.0001). Tumors were subsequently stratified for different forms of systemic therapy (none, endocrine or cytotoxic treatment) and analyzed regarding their follow up data.

Since high proliferation is commonly used as a predictor of the effectiveness of cyctoxic therapy, we analyzed if there are differences between SCL and Non-SCL tumors stratified according to their proliferative state. Furthermore the efficacy of endocrine treatment in high or low proliferating ER positive tumors is a matter of question for adjuvant treatment decision.

In addition to prognostic data, the predictive value of tumor classification according to stem cell like features will be discussed at the meeting.

**Conclusion:** Classification of breast cancers according to the expression of stem/progenitor cell markers identifies clinically relevant tumor groups. The observed uncoupling of the link between ER and proliferation suggests an influence on the response to endocrine therapy with important implications.

However, whether uncoupled tumors require a different type or a more aggressive therapy is not yet clear and will require future work.

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**Incremental costs of chemotherapy – Pharmacoeconomic results from the prospective adjuvant WSG-AGO Intergroup EC-DOC trial comparing an anthracycline–docetaxel sequence to CMF in node-positive breast cancer**

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**Background:** Taxane based adjuvant chemotherapy is the current standard for patients with node positive breast cancer. Compared to the older standard CMF or anthracycline containing regimens, the increase in efficacy is significant but modest. Next to clinically relevant side effects, the implementation of taxanes is associated with a relevant burden on health care resources. In the present study, we compared a modern taxane-based sequential regimen (4 × epirubicin/cyclophosphamide followed by 4 × docetaxel q21, EC-DOC) to the low-priced and less toxic CMF in patients with primary node positive breast cancer with special consideration of costs and resource consumption.

**Materials and Methods:** Data on resource consumption were obtained between 3/2000–5/2002 alongside the prospective, randomized, multicenter phase III WSG-AGO Intergroup trial (2000–2005) comparing EC-DOC to CMF or FEC. Total costs were presented from hospital provider perspective.

**Results:** A cohort of 110 patients from 38 study centers receiving a total of 1047 chemotherapy-cycle days was analyzed. The mean patient age was 52.4 years. Mean direct costs for the EC-DOC group (n = 54) totaled €8,459 per patient (95% CI: €7,785−9,132) with costs for cytostatics being the largest burden (€5,673, i.e. 67%). In contrast CMF was significantly less expensive (−41.2%) with mean costs of €4,973 (95% CI: €4,706−5,240). Rehospitalisation associated to toxicity was reduced by half in the CMF group (CMF: n = 4, EC-DOC: n = 8).

**Conclusions:** Our results picture a substantial budget increase attributable to introduction of taxanes to adjuvant chemotherapy of early breast cancer. The provided data will allow health economic evaluations in the context of modern individualized chemotherapy strategies.

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**Extended adjuvant (EA) endocrine therapy – Tamoxifen (TAM) or an aromatase inhibitor (AI)?**

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**Background:** The second 5 years after TAM therapy for hormone-sensitive breast cancer is associated with a rate of relapse of about 10% (node-negative), 16% (1−3 positive nodes), and 32% (4−9 positive nodes). Previous studies have shown that TAM use >5 years was not efficacious, and this is currently not recommended. MA.17, ABCSG, and NSABP B-33 explored EA therapy (EAT) with AIs, and ATLAS explored EAT with TAM. Preliminary results from ATLAS found that EAT after 5 years of TAM reduces late recurrence risk, which may now raise questions of the appropriate EAT (AI or TAM).

**Methods:** Results from the 2 large randomized trials (MA.17 and ATLAS) were compared. MA.17 randomized 5187 postmenopausal women who completed 5 years of TAM with 5 years of letrozole (LET) or placebo (PLA). The primary endpoint was disease-free survival (DFS). ATLAS randomized approximately 11,500 patients who completed 5 years of TAM to a further 5 years of TAM or not (control). Mortality and recurrence, including contralateral breast cancer, were assessed.

**Results:** At 30 months' median follow-up (FU) in MA.17, LET was associated with significantly improved disease-free survival (DFS) (hazard ratio [HR] = 0.58) and distant DFS (DDFS; HR = 0.60) vs PLA, and LET was found to be safe and well tolerated. At 50.4 months' mean FU in ATLAS, TAM was associated with a significantly lower recurrence rate vs control (HR = 0.87). There was no significant difference in overall survival in either trial. DDFS and toxicity were not reported in ATLAS and thus cannot be compared with MA.17 results.

**Conclusions:** Hormone-positive breast cancer is associated with a high rate of late relapse, and extending the duration of adjuvant therapy is beneficial. Adverse events (AEs) have not been reported for ATLAS, but previous studies of the long-term use of TAM have been associated with serious AEs. Particularly in postmenopausal women who are eligible for AIs, the risk-benefit ratio does not justify using TAM >5 years without further safety data, but ATLAS provides further rationale for EAT. A 40% DDFS improvement with EAT LET should translate into improved patient outcomes. After 5 years of TAM, EA LET is safe and associated with a greater reduction in late relapse risk and appears to offer a greater benefit than 5 additional years of TAM.

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**Expression of estrogen receptor (ER) in disseminated tumor cells of breast cancer patients**

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**Background:** The presence of disseminated tumor cells (DTC) in bone marrow (BM) of primary breast cancer patients is associated with poor prognosis. These patients may benefit from adjuvant endocrine therapy since cytotoxic agents are not able to eliminate DTCs completely as previously shown. The ERα status is routinely defined in primary tumor tissue and only patients with hormone receptor positive breast cancer are eligible for hormonal treatment. However, the ERα status of DTC may differ compared to the primary tumor. Therefore, the aims of this study were (1) to determine the ERα status of DTC in BM of breast cancer patients, and (2) to compare the ERα status of DTC and corresponding primary tumors.

**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 $2\times10^6$ 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.