and Carboxyterminal crosslinked telopeptide of type I collagen (ictp) before treatment, 3 months and 15 months after treatment were measured with commercially available test kits. Also, 34 out of 79 evaluable patients completed Functional Assessment of Cancer Therapy core questionnaire (FACT-G) with its additional breast cancer subscale (BCS) at baseline, 4, 8, 12 weeks after NHT. Incomplete questionnaires were included for cross-sectional analysis.

Results: BMD at the femur for group A patients did not change after 24 months but it was lowered for group C patients and raised for group B patients. The values for group B patients was significantly greater than group A ($p = 0.011$) and C patients ($p = 0.003$). Changes for bap at 3 months and ictp at 3 and 15 months were not different between 3 groups. However, the changes of bap at 12 months were higher in group B patients than the other groups. The difference between group B and A patients were statistically insignificant but was significant between group B and C patients ($p = 0.017$). FACT-G scores and FACT-B scores (sum of FACT-G and BCS scores) did not show statistical significance among groups, but BCS scores of group A patients were significantly higher than that of group C patients 12 weeks after treatment ($p = 0.021$). Negative changes of FACT-B and FACT-G scores were observed in group B and C patients, but positive changes in group A patients after 4 weeks of treatment. Significant difference of FACT-B score ($p = 0.008$) and FACT-G score ($p = 0.019$) were observed at that time point.

Conclusion: The sub-study suggested that impact on BMD and bone turnover proteins as well as QoL might be different in patients receiving combination of steroidal aromatase inhibitor and cyclo-oxygenase-2 inhibitor preoperatively.

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Chemotherapy-induced amenorrhea and adjuvant endocrine therapy for premenopausal women with early breast cancer

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Background: Amenorrhea is a common side-effect to chemotherapy of premenopausal women. The incidence of chemotherapy-induced amenorrhea (CIA) varies depending on the patients' age, dose and the type of chemotherapy. CIA affects choice of hormonal therapy and fertility. Menopausal status is important to determine adjuvant endocrine therapy for hormone receptor (HR)-positive women who received chemotherapy.

Patients and Methods: From September 2004 to June 2008, 60 premenopausal women who received adjuvant chemotherapy were available for the analysis. Thirty patients were treated with anthracycline-based chemotherapy and 30 with a combination of anthracyclines and taxanes. Menstrual status was monitored and serum estradiol (E2) and follicular stimulating hormone (FSH) levels were measured after the end of adjuvant chemotherapy.

Results: The patients were divided into three groups by menstruation and E2/FSH levels: 12 women (20%) in the premenoposal group (menstruation continue all courses and end of chemotherapy), 16 women (27%) in the E2 premenoposal group (cessation of menstruation but the serum E2 was within premenopausal level at the end of chemotherapy) and 32 women (52%) in the postmenopausal group (cessation of menstruation and the serum E2 was postmenopausal level at the end of chemotherapy). The median age of the patients in the premenopausal group, the E2 premenopausal group and the postmenopausal group was 35.6, 41.2 and 47.7, respectively. The patients in the postmenopausal group were significantly ($p < 0.05$) older than those in the premenopausal or in the E2 premenopausal group. Cessation of menstruation was present in 73% of patients treated with anthracyclines and in 87% of patients treated with anthracyclines and taxanes. Seven of 9 HR-positive women in the premenoposal group received tamoxifen and GnRH agonist. The other 2 patients received tamoxifen alone and become menopause. Seven of 11 HR-positive women in the E2 premenoposal group received tamoxifen and GnRH agonist. Three of 4 women who received tamoxifen alone resumed menses. Four of 5 HR-negative women the E2 premenoposal group who did not receive endocrine therapy resumed menses. Two of 26 HR-positive women in the postmenopausal group received tamoxifen and GnRH agonist treatment, 13 received tamoxifen alone, and 11 patients received aromatase inhibitor (AI). One patient in the postmenopausal group who received AI resumed menstruation. Six patients of HR-negative in the postmenopausal group continued amenorrhea.

Conclusions: In the premenopausal patients who received adjuvant chemotherapy, age and the level of serum E2/FSH are important to determine menopausal status and chose followed endocrine therapy.

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Molecular and cellular basis of anti-estrogen behavior in breast cancer cells

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Background: Breast cancer is the most common type of malignancy among women in the world. Approximately 70% of breast tumours express the estrogen receptor alpha (ERα) and are considered hormone-responsive. Endocrine therapies have long been the treatment of choice. However, the estrogen-like agonist effect and development of resistance of the available selective estrogen receptor modulator such as tamoxifen require developing new treatments that act through different mechanisms. The objective of our study is to design tools that can help to understand the molecular mechanisms involved in ligand-dependent modulation or degradation of ERα.

Materials and Methods: We selected a set of anti-estrogens with different structures and compared their effect in breast cancer cell lines on:

1. ERα degradation
2. Intra-cellular localisation of ERα
3. Regulation of transcription of ERα- endogenous target genes
4. Regulation of transcription by mutants of the ERα

Results: Using this mechanistic study we could classify the tested anti-estrogens into three groups based on their function: SERM, SERD and a new group for EM652. SERM (selective estrogen receptor modulator) include compounds such as OH-tamoxifen and RU39411, that stabilise ERα, that re-localize ERα into the nucleus upon binding, that increase transcriptional activity in mutants affecting the recruitment of cofactors or the binding of their side chain and that lack inhibitory capacities of the basal expression of endogenous genes. SERD (selective estrogen receptor modulator) include compounds such as ICI182780 or RU58668, which induce nuclear proteasome-dependent degradation ERa which occur in large nuclear foci that colocalize with the proteasome and that inhibit basal gene expression of the endogenous progesterone receptor gene (PGR). Finally, EM652 was found to affect ERα degradation and localisation similarly to SERM but inhibited basal gene expression of the endogenous PGR.

Conclusions: This approach can be used to screen the newly designed compounds based on specific antiestrogen structural features.

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Low frequency of breast cancer recurrence following introduction of adjuvant trastuzumab in HER-2 positive early breast cancer: an audit of relapses in a UK Cancer Centre and the implications for future practice

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Introduction: In England and Wales, Trastuzumab (Herceptin™) was endorsed by NICE (National Institute for Health and Clinical Excellence) for use in advanced breast cancer (ABC) in March 2002 and for early breast cancer (EBC) in August 2006. However, following publication of the first adjuvant trastuzumab studies in October 2005, there was rapid uptake of its use in the adjuvant setting prior to licensing and NICE approval. Revised NICE guidance in February 2009 suggested there was insufficient evidence to recommend Trastuzumab in ABC following use in EBC.

Method: The case notes of HER-2-positive EBC patients treated with adjuvant trastuzumab following standard chemotherapy in Newcastle between January 2006 and April 2009 were reviewed. Relapses following adjuvant trastuzumab were examined including demographic data, the time from chemotherapy to relapse and outcome of treatment for ABC. We assessed retrospectively if patients would have been eligible for the HERA trial, the model for UK practice.

Results: 95 patients received adjuvant trastuzumab. There have been 4 relapses following adjuvant chemotherapy and trastuzumab. Of the 4 patients, one would have been eligible for inclusion in the HERA trial with the others excluded on the basis of locally recurrent disease and previous non-breast malignancy (1), inflammatory disease (1) and T4 disease (1). In the HERA eligible patient, relapse occurred 9 months after completion of Trastuzumab. She was treated with trastuzumab containing therapy and lived for 13 months following relapse. Two of the other relapses occurred during trastuzumab therapy. Both of these patients has rapidly progressive disease and died 1 and 7 months after the diagnosis of recurrence. The final patient relapsed 21 months after completion of trastuzumab for local recurrence and is responding to a further trastuzumab containing regimen.

Conclusion: Relapses following adjuvant trastuzumab are rare in our dataset although follow up of these patients is short. Relapse during treatment appears to be associated with poor outcome. However,

the successful treatment of patients following completion of adjuvant trastuzumab suggests a role for trastuzumab rechallenge. Evidence for the benefit of continued anti HER-2 therapy "beyond progression" in MBC supports this approach. The scientific challenge, if recurrence is truly so rare, is to collect sufficient patient numbers to derive evidence based treatment recommendations in these patients.

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Influence of neoadjuvant chemotherapy upon survival of patients with locally advanced stage II and III breast cancer

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Background: Preoperative chemotherapy is able to improve surgical treatment by increasing the rate of breast conservation surgery. Response to preoperative chemotherapy is a predictor of long-term outcome and gives prognostic information after a short-term interval. The purpose of this study was to evaluate the extent of tumor downstaging, to determine the local regional recurrence rates, and to estimate the impact upon surgical planning and treatment strategies.

Patients and Methods: Between 2005 and 2009, 60 women with stage II or IIIA (T3N1) breast carcinoma including 19 with axillary node metastases shown on fine-needle aspiration (FNA) biopsy, were treated on three prospective neoadjuvant chemotherapy trials utilizing four cycles of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC, N = 32) or four cycles of paclitaxel (n = 28) followed by breast-conservation surgery.

Patients with significant tumor shrinkage after two cycles of chemotherapy underwent sonographically guided placement of metallic markers (n = 27) around the tumor site to facilitate later localization of the initial tumor site. After the neoadjuvant chemotherapy, patients underwent a segmental mastectomy with pathologically negative margins (n = 58) and axillary lymph node dissection. Postoperatively, all patients received four additional cycles of FAC. Postoperative radiotherapy was delivered to the breast after the completion of chemotherapy. The median follow-up was 32 months.

Results: The median tumor size was 3.5 cm at presentation and only 1.2 cm after neoadjuvant treatment. The primary tumor could not be palpated after chemotherapy in 25 patients (41.6%) of 60 patients presenting with a palpable mass and therefore required needle localization or ultrasound guidance for surgical resection. The response of primary tumor to neo-adjuvant chemotherapy was 58.3%, complete response 18% and partial response 50%. Patients with primary tumors $\leqslant$2 cm were significantly more likely than patients with larger tumors to have complete eradication of the primary tumor prior to surgery ($P < 0.001$). The 5-year local-regional recurrence rate was 3.6%. The median time to local-regional recurrence was 21 months.

Conclusion: These results suggest that primary (neoadjuvant) systemic therapy for locally advanced, stage II and stage III breast cancer may have a potential survival benefit. Neo-adjuvant chemotherapy resulted in significant down staging of breast cancer.

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Neoadjuvant doxorubicin/cyclophosphamide followed by weekly paclitaxel for operable or locally advanced breast cancer: outcome analysis of 72 patients treated at a single institution

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Background: To determine the response rate, treatment toxicity and survival of patients (pts) with operable or locally advanced breast cancer (OLABC) treated with neoadjuvant doxorubicin-cyclophosphamide (AC) followed by weekly paclitaxel (T).

Material and Methods: Between April 2003 and March 2006, 72 newly diagnosed pts with OLABC entered the treatment program, consisting of doxorubicin 60 mg/m^{2}and cyclophosphamide 600 mg/m^2 every three weeks for 4 cycles followed by paclitaxel 80 mg/m^2/week administered for 12 weeks. Eligibility criteria included early stage breast cancer (BC) with extent of local disease precluding cosmetically acceptable breast conservation (BCT), or locally advanced BC; and adequate hematologic, renal and cardiac function. Median age 49 (range 23−72) years. Clinical stage: T2 − 22.2%, T3 − 57% and T4 − 12.5%; N0 − 25%, N1,2 − 75%. Estrogen receptor (ER) positive (pos) − 52 (72.2%). Triple negative (neg) − 11 (15.3%). Post-operatively pts received radiotherapy and endocrine therapy as per standard indications. Of the 15 (20.7%) pts with Her-2 positive tumors 7 (8.7%) received trastuzumab for one year.

Results: All 72 pts were evaluable for response and toxicity. Median follow-up was 48.5 (range 7−72) months. BCT was achieved in 38 (52.8%) of pts. Clinical complete response was recorded in 7 (9.7%) pts after AC and 26 (36.1%) pts after T. The overall pathologic complete response (pCR) rate was 13.9% (95% Confidence Interval (CI) 6.9%-24.1%). In the ER pos group the pCR rate was 5.8% (95% CI 1.2–15.9%) and in the ER neg group 35% (95% CI 15.4–59.2%). Five-year overall survival and disease free survival for the entire cohort was 76% and 62%, respectively. All side effects were well manageable. There were no treatment related deaths. Neutropenic fever occurred in 10 pts (13.9%). Grade III−IV myalgia and grade III−IV neutropenia were noted in 7 (9.7%) pts each.

Conclusion: The overall pCR rate and its CI include values previously reported for doxorubicin and taxane containing regimens. AC-weekly T is a well tolerated preoperative regimen suitable for routine practice which enables BCT in a majority of pts. A large proportion of pts, particularly with ER pos tumors do not achieve pCR. New approaches such as tailoring of therapy to the molecular signature of the tumor may improve results.

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Exemestane in primary breast cancer patients who are eligible to receive neoadjuvant hormonal therapy

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Background: Primary hormonal therapies have demonstrated great activity in elderly women with locally advanced and hormone-dependent breast tumors. However, there is not so much information in operable disease specially outside elderly population. Exemestane, an esteroidal aromatase inhibitor, has demonstrated activity in the adjuvant and in the metastatic setting; smaller trials have also shown its efficacy in the neoadjuvant setting. The primary aim of this multicentre study was to analyze the efficacy of exemestane as a neoadjuvant treatment.

Material and Methods: Postmenopausal breast cancer patients (pts) with histologic diagnosis of infiltrating breast carcinoma and tumors expressing >50% ER+ were eligible. Tumor had to be measurable at least in one dimension by clinical exam, ECO, Mammography or MRI; no previous hormonal treatment/chemotherapy was permitted. At baseline, all p were considered non-eligible for breast-conserving surgery. Response was estimated by mammography and/or MRI every 3 months (RECIST criteria). Secondary endpoints were rate of breast-conserving surgery and rate of Patological Complete Response. Consecutive eligible pts received oral exemestane 25 mg/d for 6 months before surgery, unless disease progression or unacceptable toxicity were seen.

Results: 68 pts were included in the study. Patient characteristics were median age 83 (56.5–93.9); tumor stage: T1: 11, T2: 22, T3: 9 and T4: 11; nodal involvement was N0: 20, N1: 7, N2: 5 and N3: 2; tumor grade I:11, II: 24, III: 6 and 7 unknown. 38 pts have been evaluated for response, 7 were lost of follow up and 3 were screening failure and 1 remain in treatment (end 20 Nov). Up to date, 4 CRs (10.5%) and 27 PRs (71%), 4 SD (10.5%) and 3 PD (8%) out of 38 evaluable pts by any of the imaging methods or clinical exam.

At the time of this analysis, only 9 pts have been recovered for breast surgery and 6 continue with hormonotherapy for different reasons. Surgery offered to these pts were conservative in 4 pts and mastectomy in 5 pts. Partial pathologic remission was seen in 8 pts and in 1 there was a progression. During exemestane treatment one patient was changed to Letrozol due to toxicity.

Conclusions: Exemestane was found to be a well-tolerated and effective neoadjuvant treatment in elderly patients with a breast cancer tumor. Follow-up regarding the proportion of conservative surgery will be available shortly.