HR+EBC receiving 3 y of goserelin and (1) adjuvant ET (tamoxifen or anastrozole); or (2) adjuvant ET plus ZOL q6m. Cost-effectiveness was measured as the incremental cost per quality adjusted life year (QALY) gained. Probabilities of breast cancer recurrence were from the Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12). Other probabilities and costs specific to each country were from the published literature. Results were generated under two scenarios: (1) benefits of ZOL persist to the 7-y maximum follow-up in ABCSG-12 (trial benefit); (2) benefits persist until recurrence or death (lifetime benefit).

Results: Expected costs of 3 y of ZOL q6m (medication and administration) were €2,300 for Portugal, €2,100 for Spain, and €1,500 for Italy. Under the trial benefits scenario, these costs were partially offset by savings in treatment of breast cancer recurrence of €200 for Portugal and €900 for both Spain and Italy. ZOL was therefore projected to increase total costs by €2100 for Portugal, €1300 for Spain, and €600 for Italy. Projected QALYs gains with ZOL were 0.33 for Portugal, 0.47 for Spain and 0.46 for Italy. Cost per QALY gained was €6364 for Portugal, €2766 for Spain, and €1304 for Italy (all favorable). Assuming lifetime benefits, savings from preventing breast cancer recurrences completely offset ZOL costs for Spain and Italy, with ZOL yielding net savings of €2100 and €2900 respectively. Incremental total costs were €1400 for Portugal. Projected QALYs gains with ZOL were 0.96 for Portugal, 1.59 for Spain, and 1.57 for Italy. ZOL was therefore dominant (lower costs and more QALYs) for Spain and Italy; the cost per QALY gained for Portugal was highly favorable (€1,458).

Conclusion: Adding ZOL to ET in premenopausal women with HR+EBC is highly cost-effective (<€50,000 per QALY gained) from the healthcare system perspectives of Portugal, Spain, and Italy even under conservative assumptions regarding duration of ZOL benefits. ZOL may be cost saving in Italy and Spain if benefits persist >7 years.

20 Poster

Impact of fulvestrant 500 mg/month versus fulvestrant 250 mg/month on bone turnover markers and endometrial thickness: findings from the NEWEST study

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Background: Fulvestrant (FASLODEX™) is a selective oestrogen receptor (ER) antagonist with no agonist effects used to treat postmenopausal women with advanced breast cancer at 250 mg/month (F250). Studies have suggested that increasing the dose may enhance ER blockade and improve efficacy. The NEWEST (Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumours) study compared the activity of a higher-dose fulvestrant regimen (F500, 500 mg/month plus 500 mg on Day 14 of Month 1) with F250 as neoadjuvant therapy. To collect further tolerability data for F500 vs F250, their effects on bone and endometrium were investigated.

Material and Methods: NEWEST was a Phase II, randomised, open-label, multicentre, 16-week study (9238IL/0065/NCT00093002) of F500 vs F250 in postmenopausal women with ER+, locally advanced breast cancer. Secondary objectives included comparisons of F500 vs F250 on tolerability, endometrial thickness and serum bone markers. Adverse events (AEs) were recorded throughout the study. Changes from baseline to week 16 in endometrial thickness were assessed by transvaginal ultrasound. Serum bone turnover markers (bone-specific alkaline phosphatase [ALP], C-terminal telopeptides of Type 1 collagen [CTX-1] and procollagen Type 1 N propeptide [PINP]) were measured at baseline and every four weeks until surgery (week 16).

Secondary outcome measure	n	Fulvestrant F500 (N = 107)	n	Fulvestrant F250 (N = 101)
Treatment-related SAEs, n (%)		1 (0.9)		3 (3.0)
Treatment-related AEs, n (%)		40 (37.4)		31 (30.7)
Mean change in endometrial thickness (mm), from baseline to week 16				
Patients with any baseline value	46	−1.34	44	−1.10
Patients with baseline value ⩽5 mm	37	−0.03	30	−0.18
Mean change in bone turnover markers, from baseline to week 16				
ALP (μg/L)	73	−0.36	73	−0.15
CTX-1 (ng/mL)	71	+0.02	70	+0.04
PINP (μg/L)	72	−0.35	72	+0.35

Results: In total, 211 women participated (F500 109; F250 102). Key tolerability data are shown below. Treatment-related serious AEs (SAEs) were rare; none led to withdrawal. From baseline to week 16, there were small, non-significant reductions in endometrial thickness (any baseline value) in both treatment groups. Bone turnover markers remained stable throughout the study.

Conclusions: F500 and F250 were well tolerated, with no adverse effects on endometrial thickness or bone turnover markers, indicating no ER agonist effects. The lack of impact on bone suggests a potentially good long-term tolerability profile for F500.

22 Poster

First interim analysis of a randomized trial comparing capecitabine/epirubicin/cyclophosphamide (XEC) vs 5-FU/epirubicin/cyclophosphamide (FEC) as adjuvant therapy for medium- or high-risk early breast cancer (EBC)

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Background: Capecitabine is widely used as first-line therapy for metastatic breast cancer because of its high efficacy and good tolerability. Anthracyclines combined with 5-FU and cyclophosphamide are now a post-operative standard of care for medium-/high-risk EBC. We are comparing safety and efficacy of capecitabine or 5-FU combined with epirubicin and cyclophosphamide as postoperative (adjuvant) chemotherapy for EBC.

Patients and Methods: Women with node-positive or high-risk node-negative EBC are eligible for the trial. The planned sample size is 1000 patients (500 in the XEC arm, 500 in the FEC arm). The primary study objectives are to evaluate safety (NCI CTC version 3.0) and to assess 1-, 2-, and 3-year disease-free survival (DFS) rates. Overall survival is a secondary endpoint. Patients are randomised to receive either XEC (capecitabine 1000 mg/m^2 bid, d1−14 + epirubicin 75−90 mg/m^2 iv, d1 + cyclophosphamide 600 mg/m^2 iv, d1) or FEC (5-FU 500 mg/m^2 iv, d1 + epirubicin 75−90 mg/m^2 iv, d1 + cyclophosphamide 600 mg/m^2 iv, d1). In both arms, treatment is given every 3 weeks for up to 6 cycles. After completion of adjuvant chemotherapy, patients can receive radiotherapy at the investigator's discretion. Patients with hormone receptor-positive disease may receive endocrine therapy after completing adjuvant chemotherapy.

Results: By May 2009, 246 patients had been enrolled in the XEC arm and 209 in the FEC arm, all of whom are included in the intent-to-treat analysis reported here. The baseline characteristics are well balanced in the two treatment arms. After 2 years' follow-up, 1- and 2-year DFS rates are 89.24% and 61.78%, respectively, in the XEC arm, and 84.69% and 33.12%, respectively, in the FEC arm. 1-year overall survival rates are 96.03% with XEC and 93.68% with FEC. The two regimens show differing safety profiles. The incidences of all-grade adverse events with XEC and FEC, respectively, are: alopecia (6% vs 11%); hand-foot syndrome (4% vs 0%); and upper respiratory tract infection (0% vs 1%). Severe adverse events to date are neutropenia (2 cases with XEC vs 4 cases with FEC) and abnormal hepatic function (2 cases vs 0 cases, respectively). There have been no cases of severe hand-foot syndrome.

Conclusions: These interim results suggest that the risk of breast cancer recurrence can be reduced by replacing 5-FU with capecitabine in an anthracycline-based adjuvant regimen. The high activity of XEC is achieved with good tolerability.

23 Poster

Pregnancy-associated breast cancer is as chemosensitive as classic breast cancer in the neoadjuvant setting

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Purpose: To determine the chemosensitivity of pregnancy-associated breast cancer (PABC) in the neoadjuvant setting.

Patients and Methods: Data on 57 PABC patients who received neoadjuvant chemotherapy (NACT) were collected. To evaluate the theoretical response rate to chemotherapy, we used well-calibrated logistic regression-based nomograms that have been previously developed to calculate individual probability of pathologic complete response (pCR) according to the chemotherapy regimen given. Theoretical and observed pCR rates were analyzed in terms of discrimination and calibration.

Results: Observed rates of pCR were concordant with predictions in the whole population and in the subgroups that were analyzed. For the whole population, the area under (AUC) the receiver-operated curve (ROC) was 0.77 (95% CI, 0.66–0.87). The calibration of predicted and observed probabilities was excellent, with no statistical difference (P = 0.77). In the subgroup analysis (NACT initiated during pregnancy or postpartum, NACT with only anthracycline or both anthracycline and taxanes), discriminations assessed by AUC were significantly above 0.5, except for patients treated with anthracycline-only NACT. The calibration curves were satisfactory but chemosensitivity was poorer in the anthracycline-only subgroup.

Conclusion: Through the use of nomograms, our study demonstrates that PABC is as chemosensitive as classic breast cancer and suggests that taxanes should be part of the NACT regimen for PABC.

24 Poster

Zoledronic acid (ZOL) as add-on therapy in patients with tumour residuals after neoadjuvant chemotherapy for primary breast cancer − first interim safety analysis of the NATAN study (GBG 36)

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Background: Patients (P) with residual disease after neoadjuvant chemotherapy (NACT) are considered to be chemo-resistant. There is growing evidence, that ZOL has beneficial effects in the metastatic and adjuvant treatment.

Patients and Methods: P who had invasive tumor residuals after a minimum of 4 cycles of an anthracycline/taxane containing NACT were eligible. P were randomized to receive ZOL 4 mg i.v. vs. observation. ZOL was given for the first 6 months (mos) q 4 wks, q 3 mos the following 2 yrs, and q 6 mos for the last 2.5 yrs. Postmenopausal P with hormone receptor (HR)-pos BC received letrozole, premenopausal P received tamoxifen. HER2-pos P received trastuzumab since an amendment in 2007.

Primary objective is the event-free survival after 5 yrs of ZOL vs. observation. The total number of P required for the trial is equal to 654 to observe 316 events after the end of follow up.

As the safety of long term use of ZOL in this population is not fully characterized, a pre-planned interim safety analysis was performed after the first 100 P received ZOL for 2 yrs.

Results: Between 2/2005 and 5/2009 693 P were enrolled. Time between surgery and randomization was <4 mos in 48.4%, 4−12 mos in 34.5%, and 13−36 mos in 17.1% of P. The median age was 50.9 yrs (range 33.7–88.2), 72.3% of P were postmenopausal. 82% had HR-pos and 19% HER2-pos BC.

99 of 100 P started ZOL therapy. After a 2 yrs interval, 75 P (75%) were still under treatment, 70 received the full dose and 5 stopped therapy due to relapse. 24 P (24%) discontinued the study early due to toxicity (3), withdrawal of consent (5), patient's wish (7), death (1, not related to medication) and administrative reasons (8). During the first 2 yrs, a total of 23 AEs were reported due to joint pain (39%), headache (17%), vertigo & chills (each 13%), hot flushes (9%), hypocalcaemia & circulation problems (each 4%). Treatment delays occurred in 50% (median 6 d, range: 1 to >50 d).

Conclusion: This is the first post-neoadjuvant phase III study. No unexpected AEs and no osteonecrosis of the jaw were reported, demonstrating that long term ZOL is feasible in this setting. The first interim efficacy analysis is expected in 2011.

25 Poster

Influence of pathologic tumour characteristics on ipsilateral breast tumour recurrences after breast conservation and neoadjuvant chemotherapy

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Background: It has been reported that breast conservation after neadjuvant chemotherapy (NAC) could be asociated with an increase in Ipsilateral Breast Tumor Recurrences (IBTR) rates. The purpose of this study is to determine incidence and prognostic factors of IBTR in patients with breast conservation after NAC.

Materials and Methods: Using our breast cancer (BC) data base we identified 173 women treated with NAC followed by lumpectomy between 1998 and 2009. Clinical stage (TNM) at diagnosis was stage I in 1.2%, stage IIa in 49.4%, stage IIb in 32.6% and stage III in 16.8%. NAC was based on anthracyclines plus taxanes in 67.4% of cases. All patients had negative resection margins (24.6% required rexcision by second surgery). All patients were treated with adjuvant external-beam radiation therapy to the affected breast, (median delivered dose 50 Gy) followed by boost to tumor bed with external radiotherapy in 33% or interstitial brachytherapy in 53.8% of cases. Internal mamary or supraclavicular node radiation was administered in 8.1% and 44.8% of patients respectevely.

Results: At a median follow up of 50 months, 7 patients (4%) developed IBTR. Actuarial IBTR free was 96.7% (±3%) at 4 year. Variables asociated with increased IBTR were: ER negative vs ER positive (4 year IBTR free 92% vs 100%, p = 0.02), HER2 positive vs HER2 negative (4 year IBTR free 87% vs 100%, p = 0.001), pCR vs no pCR (4 year IBTR free 93% vs 100%, p = 0.02), Multifocal pattern of residual disease vs sollitary mass (4 year IBTR free 93% vs 98%, p = 0.06). Others analyzed variables that didn't show association with IBTR were residual tumor size, DCIS in specimen, lymphovascular space invasion, clincal stage at diagnosis and margin status negative at first surgery. In multivariate analysis only HER2 positive disease was associated significatively with increased IBTR (HR: 12.2 95% IC 1.3–110, p = 0.026). Five out of seven patients that experienced IBTR were HER2 positive, all of them had been treated with trastuzumab and their median time to relapse was 30 months.

Conclusions: After NAC, breast conservative surgery with negative margins followed by radiotherapy results in very low rates of IBTR. However, lumpectomy should be carefully considered in patients with HER2 positive tumor, specially pCR is not achieved after NAC.

26 Poster

Breast conserving therapy after neoadjuvant treatment: Is it oncologic safe?

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Objective: Several prospective trials report about a potentially increased risk of local recurrence free survival (LRFS) after breast conserving treatment (BCT) following neoadjuvant chemotherapy. The aim of this study was to investigate this issue at a large single cancer centre series with well documented neoadjuvant therapy and follow-up.

Method: All consecutive patients undergoing breast cancer surgery after neoadjuvant chemotherapy (3xCMF or4−6x EC) between 1995 and 2007 were included. Subjects were separated into three groups, group 1 was scheduled for mastectomy and eventually was mastectomized (MX-MX), group 2 was scheduled for mastectomy but received BCT (MX-BCT) and group 3 was scheduled for BCT before and received BCT after neoadjuvant treatment (BCT-BCT). Indications for mastectomy were no change or progressive disease, inflammatory breast cancer and multicentricity as well as R1 resection after several attempts of breast conservation.

Results: 308 patients were included in the analysis. The median follow up were 60 months. Overall and distant recurrence free survival (OS and DRFS) was worse (both p = 0.001) in MX-MX patients (OS: 76%; DRFS: 58%) compared with MX-BCT (OS:91%; DRFS: 78%) and BCT-BCT patients (OS: 95%; DRFS: 87%). There was only a non-significant trend for an increased LRFS in downsized patients (MX-BCT=87%; BCT-BCT=96%; MX-MX=91%; p = 0.07). This difference was mainly due to the comparison