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.

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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.

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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.

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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

between MX-BCT and BCT-BCT ($p = 0.04$) while there was no significant difference when comparing MX-MX versus MX-BCT patients ($p = 0.79$). Multivariate analyses using surgical group, menopause, lymph node status, grading, pathological response, tumor type, endocrine responsiveness and her2neu status demonstrated no influence of any of these parameters on LRFS. Surgical group (BCT), lymph node status (N0) and grading (G1/2) were predictive for OS while tumor type (ductal), lymph node status (N0) and grading (G1/2) were predictive for DRFS.

Conclusion: There was no significant difference in LRFS, DRFS and OS in patients downsized from mastectomy to breast conservation by neoadjuvant chemotherapy. This was independent of menopause status, endocrine responsiveness, tumor type and pathological response. Thus, BCT is safe after tumor downsizing with neoadjuvant therapy.

MX-BCT: Patient scheduled for mastectomy receiving breast conservation

MX-MX: Patient scheduled for mastectomy receiving mastectomy

BCT-BCT: Patient scheduled for breast conservation receiving breast conservation

LRFS: Local recurrence free survival

DRFS: Distant recurrence free survival

OS: Overall survival

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Intrinsic Susceptibility-Weighted MRI is an effective method of evaluating tumour oxygenation in primary breast cancer and can predict for response to neoadjuvant chemotherapy

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Background: Intrinsic Susceptibility-Weighted MRI (ISW-MRI), also known as Blood oxygenation level dependent (BOLD) MRI, can provide important functional information about whole tumour oxygenation. Higher values of R_2* (the apparent transverse relaxation rate calculated from ISW-MRI data) imply a more hypoxic tumour environment. This study explores the relationships between pretreatment R_2* and tumour characteristics, and assesses whether changes in R_2* correlate with final clinical and pathological response to neoadjuvant chemotherapy (NAC) in breast cancer (BC).

Materials and Methods: 83 pts with primary BC were selected to undergo dynamic contrast-enhanced MRI (DCE-MRI) and ISW-MRI before and after 2 cycles of NAC. Diffusely infiltrating, necrotic or invasive lobular carcinomas (ILC) were excluded due to paradoxical changes in R_2*. DCE-MRI T_1 & T_2-weighted kinetic parameters (K^{trans}, v_e, k_{ep}, $IAUGC_{60}$, relative blood flow (rBF) & volume (rBV), MTT) and R_2* were obtained for whole tumour regions of interest. Relationships between tumour characteristics (grade, size, ER/PR/HER2 status), MRI kinetic parameters and pretreatment R_2* were assessed using Spearman's rank correlation for continuous variables and the Mann-Whitney U test for discrete variables. Pretreatment and changes in R_2* were correlated with final pathological and clinical response to NAC using paired t-testing.

Results: 31 pts (T2−4, N0−2, M0; median age 44, range 22−62) were available for pretreatment and 27 for response assessment. 37 with ILC, ill-defined or necrotic tumours were excluded, 12 did not undergo their first MRI (mainly due to claustrophobia), 1 had only axillary nodal disease visible, 2 had corrupted MRIs that were not analysable and 4 did not have their repeat MRI. 15 pts received anthracycline based NAC and 12 docetaxel NAC. There were no correlations observed between pretreatment R_2* and tumour characteristics or response. Both rBF & rBV were inversely correlated with R_2* ($r = -0.51$, $p = 0.006$; $r = -0.46$, $p = 0.015$), this correlation disappearing with NAC ($r = -0.39$, $p = 0.112$; $r = -0.37$, $p = 0.081$). There were 16 pathological responders & 11 non-responders, and 23 clinical responders & 4 non-responders. Significant R_2* increases were seen with NAC ($34.8s^{-1}$ vs $-31.1s^{-1}$, $p = 0.006$) with larger increases predicting for final pathological ($36.5s^{-1}$ vs $31.7s^{-1}$, $p = 0.025$) and clinical response ($35.5s^{-1}$ vs $31.7s^{-1}$, $p = 0.017$).

Conclusions: Pretreatment R_2* relates to blood rather than tumour oxygenation as suggested by its relationship with blood volume and flow. With the loss of this relationship after NAC, R_2* may become a more reliable marker of actual tumour hypoxia. Furthermore, responders to treatment displayed more hypoxic cancers after 2 cycles of NAC. ISW-MRI has the potential to predict not only therapy response but to identify those who may benefit most from hypoxia targeting agents.

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Applying survival based cost-effectiveness analyses to estimate the impact of patent expiry on the cost-effectiveness of letrozole and anastrozole versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer

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Background: The latest update of the BIG 1-98 study (76 months) reports a hazard ratio for overall survival (OS) of 0.83 (95% CI 0.71–0.97) for 5yrs letrozole (LET) vs tamoxifen (TAM) (censoring TAM patients who crossed over to LET). At 100 months, ATAC remains to show a significant OS benefit for anastrozole (ANA) compared to TAM. A new framework for the economic analysis of the aromatase inhibitors (AIs) uses observed differences in OS to estimate the incremental cost per life year (LY), and per quality adjusted LY (QALY) gained of 5 years LET versus 5 years TAM, and 5 years ANA vs 5yrs TAM in ER+ postmenopausal women, from a UK NHS perspective, incorporating possible price reductions due to patent expiry for both AIs.

Methods: Survival probabilities over the 1st 7 years post-surgery were extracted from BIG 1-98, and extrapolated to 20 years using data reported by the Early Breast Cancer Trialists' Group for women receiving 5 years TAM. HRs for LET and ANA were applied to TAM event rates for the first 7 and 9 years, respectively. Conservatively, equivalent annual survival probabilities were assumed thereafter. Reduced ANA costs, to account for generic ANA, were applied from year 1, and reduced LET costs, to account for generic LET, from year 2. Two scenarios were considered for the price of generics; scenario 1 assumed a 50% price reduction and scenario 2 a 70% price reduction. Adverse event (AE) cost and five year costs for locoregional recurrence (LR) and metastases (METS) were also applied. A QALY model applied published utility weights for DFS with AEs, LR, and METS. All costs and health benefits were discounted at 3.5% annually.

Results: For LET, the reference case results show that over a 20 year period, the incremental cost per QALY gained (ICQ) is £9,287, with an upper 95% CI of £32,576. Assuming a 50% price reduction from the 2nd year of treatment lowers the ICQ to £4,727. For ANA, the reference case ICQ is £44,294, with an upper 95% CI of TAM dominating ANA [Table 1]. Assuming a 50% price reduction from the 1st year of treatment lowers the ICQ to £16,099. These results suggest that use of LET is a more cost-effective use of healthcare resource, despite the fact that ANA loss of patent will occur one year prior to LET. The clinical benefits associated with LET far outweigh any cost saving resulting from a lower ANA price for 12 months.

Table 1: Incremental cost per QALY gain for Letrozole and Anastrazole

	Letrozole	Anastrazole
Base case	£9,287	£44,294
Scenario 1: Generics priced 50% below current price	£4,727	£16,099
Scenario 2: Generics priced 70% below current price	£2,902	£3,807

Conclusion: Given the extended follow-up periods for both the ATAC and BIG1−98 trials, one would hope to observe some effect on OS. Using estimates of effects with respect to OS, these new economic analyses suggest a preference for LET, with a lower cost per QALY compared to ANA, despite the shorter time to patent expiry for ANA.

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Factors predicting a pathological complete response following neoadjuvant chemotherapy for breast cancer

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Background: Patients diagnosed with large size or locally advanced breast cancer are frequently treated with neoadjuvant chemotherapy. This work establishes a model, based on demographic and clinicopathological features to predict pathologic complete response (pCR) following neoadjuvant chemotherapy.

Material and Methods: A consecutive group of 335 patients diagnosed with a primary non-metastatic large or locally advanced breast cancer, who had received neoadjuvant systemic therapy between January 2000 and May 2009 at the University Hospitals Leuven was analyzed. After exclusion of 65 patients (58 receiving neoadjuvant hormonal therapy, 4 switching over to neoadjuvant hormonal therapy and 3 refusing operation) 270 patients remained for analysis. pCR was defined as no evidence of invasive tumor in the breast and axillary lymph nodes. Residual in situ lesion without an invasive component is regarded as pCR in this study.