primary prophylaxis with (pegylated) G-CSF and secondary prophylaxis with epoetin(. Pts with tumor reduction less than 50% according to breast ultrasound were randomized to receive either 4 additional cycles TAC or 4 cycles of NX (Vinorelbine 25 mg/m day 1 + 8 plus Capecitabine 2000 mg/m day 1 14, q21(NX). Primary endpoint was sonographic tumor response before surgery. Secondary endpoints were pCR-rate (no invasive/no non-invasive residuals), breast conservation rate, safety and compliance.

Results: Between July 2002 and June 2005 more than 2000 pts were recruited into the GEPARTRIO−trial. Nearly 630 non-responder to TAC ×2 were randomized to continue TAC or to switch to NX. Median clinical tumor size amounted to 4.0 (1.0−30.0) cm at study entry. Safety and blinded efficacy interim analysis was performed on 154 TAC and 146 NX pts (operable 82.2%, locally advanced 17.8%). Sonographic response before surgery was reported in 67.7%; breast conservation in 59.2% and pCR in 5.2% of these patients. Main toxicities (grade I-IV %TAC vs %NX) were: anemia (92 vs 86), thrombopenia (37 vs 29), neutropenia (72 vs 81), febrile neutropenia (10 vs 6), infection (30 vs 23), vomiting (40 vs 23), diarrhea (44 vs 32), stomatitis (67 vs 45), edema (42 vs 37), asthenia (89 vs 85), hand-foot-syndrome (23 vs 46), allergic (18 vs 21), nail (42 vs 25), dyspnea (35 vs 28), sensory and neuropathy (49 vs 57). Treatment was discontinued in 28 pts (9.3%) due to toxicity (4 vs 7 pts), on patients request (4 vs 8) and tumor progression (4 vs 1).

Conclusions: Ongoing treatment in pts non-responding to TAC ×2 can achieve sonographic responses in 67% with the chance of breast conservation. Both chemotherapy regimens were well tolerated. NX (without G-CSF) was associated with a better toxicity profile compared to TAC (with G-CSF). The rate of pathologic complete remission was low. Results on the efficacy endpoints will be presented during the meeting.

348 Poster

A cost-utility evaluation of adjuvant hormonal options in postmenopausal women with breast cancer: A Belgian perspective

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Background: Based on recent clinical trials, Anastrozole (ANA) for 5 years, Tamoxifen followed by Exemestane for 2.5 years each (TAM-EX) and Tamoxifen for 5 years followed by Letrozole for 3 years (TAM-LET) have become acceptable alternatives to adjuvant Tamoxifen (TAM) for 5 years in postmenopausal (PM) women with hormone receptor positive (HR+) breast cancer. As these newer aromatase inhibitor strategies are associated with both improved disease-free survival and higher drug costs, an economic evaluation was undertaken to compare the relative cost-utility (CU) of ANA, TAM-EX and TAM-LET compared to TAM alone in terms of cost per quality-adjusted life year (QALY) gained.

Methods: A Markov model was developed to calculate cumulative costs and QALYs in a hypothetical cohort of 1000 PM women with HR+ early-stage breast cancer. The baseline event rate and hazard ratios for cancer recurrence and adverse events, including vaginal bleeding, endometrial malignancies, DVT/PE and fractures, were derived primarily from the ATAC, IES and MA17 trials. The primary analysis assumed a carry over benefit for adjuvant therapy beyond the hormonal treatment period. Background mortality rates were taken from Belgian life tables. Costs of hormonal therapies, breast cancer management, and adverse events were derived from an HEDM/IMS study of Belgian costs. Health state utilities were taken from the literature and supplemented by expert opinion. The model took a third-party payer perspective over 10 and 20-year time horizons. Both costs and outcomes were discounted at 3%.

Results: ANA, TAM-EX and TAM-LET were all associated with QALY gains and increased costs relative to TAM alone. CU improved over time as QALY benefits accumulated and outweighed up-front costs. At 10 years, relative to TAM alone, the CU of ANA was €48,323, TAM-EX was €14,147 and TAM-LET was €330,942. By 20 years, the CU of ANA was €19,992, TAM-EX was €4962 and TAM-LET was €10,548. Incremental CU comparisons between TAM-EX, ANA and TAM-LET were quite sensitive to relative differences in the hazard ratios and will be presented in a two-way sensitivity analysis. CU results for node negative and positive subsets will also be presented.

Conclusion: The CU of all three aromatase inhibitor strategies was favourable compared to TAM alone. Incremental comparisons among the AI options were sensitive to changes in the hazard ratios, but appeared to favour TAM-EX.

349 Poster

After 10 years of follow-up, preoperative chemotherapy is still safe in operable breast cancer: Clinical and translational results from the European Organisation for Research and Treatment of Cancer Trial 10902

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Introduction: The Preoperative Chemotherapy in Primary Operable Breast Cancer (POCOB) trial was designed to evaluate whether preoperative chemotherapy (CT) in patients with primary operable breast cancer (BC) results in better overall survival (OS) and relapse free survival (RFS) rates and whether preoperative CT allows more breast-conserving surgery (BCS) procedures than postoperative chemotherapy. Additionally, tumour tissue was collected for translational research.

Patients and Methods: Patients (n = 698) with operable BC (T1c, T2, T3, T4b, N0−1) were enrolled between 1991 and 1999 and randomised between CT administered preoperatively versus postoperatively. CT consisted of four cycles of fluorouracil, epirubicin, and cyclosphosphamide. The primary endpoint was OS, secondary endpoints being relapse-free survival (RFS) and locoregional recurrence (LRR).

Results: With a median follow-up (FU) of 117 months there was no statistically significant difference between OS (hazard ratio (HR): 1.09; 95% CI (0.83−1.42); p = 0.54), RFS (HR: 1.12; 95% CI (0.90−1.39); p = 0.29) or LRR (HR: 1.16; 95% CI (0.77−1.74); p = 0.48). Moreover, there was no statistically significant difference in time to distant progression (HR: 1.17; 95% CI (0.92−1.50); p = 0.19) and time to second primary tumour (HR: 0.86; 95% CI (0.52−1.41); p: 0.54). In the preoperative group, 37% of the patients underwent BCS in stead of a mastectomy compared to 21% of the patients in the postoperative group. With a median FU of 7 years, the p53 status was significantly correlated with the pathological tumour response and the clinical response (resp p = 0.01 and p = 0.008). Clinical tumour response was also predicted by clinical tumour size, tumour grade, p53 status, PgR status and HER2 status. There was no correlation between the p53 expression and OS (HR: 1.72; p = 0.15).

Conclusion: Preoperative chemotherapy does not change the OS, RFS or the LRR in patients with breast cancer. Moreover, after 10 years of FU, there was no statistically significant difference in time to distant progression or to second primary tumours. This implies that preoperative chemotherapy is a safe procedure for patients with early breast cancer, even after a FU period of 10 years. Furthermore, it increases the amount of BCS. This most recent up-date of the POCOB will be presented together with translational research results with a median FU of 10 years.

350 Poster

NCIC CTG MA17: Updated analysis on disease free survival (DFS) according to estrogen receptor and progesterone receptor status of the primary tumor

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Introduction: Identifying biomarkers to predict response to adjuvant aromatase inhibitor therapy is important. In the ATAC trial (anastrozole vs tamoxifen) benefit of anastrozole over tamoxifen appeared restricted to the ER+ PgR− patients and not in those with ER+ PgR+ tumors. In contrast in subgroup analysis of the BIG1−98 trial the magnitude of benefit of letrozole vs tamoxifen on DFS did not vary according to PgR status. A central review of tumor tissue is currently being performed in this trial. MA.17 randomized 5187 postmenopausal women disease free after 5 years of tamoxifen to 5 years of letrozole or placebo. After 30 months median follow-up (range 1.5−61.4 months), the hazard ratio (HR) for DFS in the overall population was 0.58 (0.45–0.76, p = 0.00004) in favor of letrozole. Almost all patients (97.4%) had estrogen receptor (ER) and/or progesterone receptor (PgR) positive primary tumors. We will present at the meeting the outcome of women according to the receptor status of their primary tumors, both in the intent to treat population of MA.17 (Letrozole and placebo patients) as

well as in the post unblinding analysis of MA-17 (Letrozole, placebo and placebo crossed over to letrozole patients)

Design and Methods: The ER and PgR values were both known in 4653 patients and retrospective exploratory analyses were conducted to compare time to recurrence in the four receptor sub-groups by ER (+/−) and PgR (+/−) status. ER and PgR positivity was defined as ⩾10 fmol/mg protein, or positive by ERICA or PgRICA.

Summary: In the ITT analysis, the DFS events according to treatment arm and receptor status are given in the table below. The DFS benefit of letrozole was clearly most pronounced in women with ER+PgR+ (HR: 0.49). Similar results were observed for distant disease free survival (DDFS) [HR: 0.53] and overall survival (OS) [HR.0.58]. The test for interaction between ER+PgR+ and ER+PgR- tumors was statistically significant for DFS (p = 0.02), and was marginally significant for DDFS (p = 0.06) and OS (p = 0.09) Adjustment for nodal status and prior adjuvant chemotherapy did not affect this result.

	n	Letrozole (L) events	Placebo (P) events	HR* L vs P (95%CI)
ER+PgR+	3809	60 (3%)	117 (6%)	0.49 (0.36–0.67)
ER+PgR−	636	19 (6%)	17 (5%)	1.21 (0.63–2.34)
ER−PgR+	200	4 (4%)	5 (5%)	0.62 (0.15–2.12)
ER−PgR−	8	–	–	–

*Hazard ratios for events in DFS (HR less than one indicates value in favor of letrozole).

Conclusions: In MA.17, the effect of LET relative to placebo appears most pronounced in women with the most hormone dependent, ER+ PgR+, tumors. Its apparent lack of benefit in patients with ER+ PgR- suggests that a functional ER is necessary for letrozole to have an effect following 5 years of tamoxifen. These results should be interpreted with caution as this was an unplanned analysis and the receptor levels were measured locally. We plan to centrally measure standard ER and PgR levels and to compare them to quantitative assessment by immunofluorescence.

351 Poster

The BASO II trial of primary treatment of tumours of excellent prognosis

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This trial examined additional treatments to Wide Local Excision with clear margins, in Grade I, node negative tumours of 2 cm or less with clear margins (Nottingham Prognostic Index ⩽ 2.4, predicted 10 year survival 96%. Between 1992 and 2000, 1158 eligible women were randomised to a 2×2 design. The primary outcome measure is local recurrence (LR), defined as tumour in the treated breast. Data has been obtained in over 90% for the censored date of August 2003 giving a median follow up of 72 months, (range 39–144).

Survival is excellent, only 16 deaths from breast cancer, giving a 10 year actuarial survival of 98%.

LR by randomisation

	n	LR	LR% PA
Radiotherapy (RT) to intact breast	570	15	0.4
No RT	568	42	1.2
Tamoxifen	214	6	0.5
No Tamoxifen	216	17	1.3
RT plus Tamoxifen	98	0	Nil
No RT, No Tamoxifen	96	10	1.7

However for those entering only to the RT or Tamoxifen comparisons, the other therapy was electively in identified centres.

Results by treatment received

Received	n	LR	LR% PA
Neither therapy	175	26	2.5
RT Only	182	10	0.9
Tamoxifen Only	421	20	0.8
RT plus Tamoxifen	380	4	0.2

Conclusion: In these tumours of least aggression:

1. A local recurrence rate of 2% per annum is too high from surgery alone.
2. Tamoxifen or RT lowered LR to acceptable levels (0.6–0.8% PA)
3. In the short term Tamoxifen is as effective as RT in lowering local recurrence.
4. Since around 20% of all screen detected cancers fall into this group this result has important cost, waiting times and workload implications for Radiotherapy units, if borne out by longer follow up.

352 Poster

Oral clodronate (Bonefos®) in women with primary breast cancer: effects on bone turnover and skeletal metastases

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Introduction: Breast cancer treatments that suppress ovarian function (hormone therapy and chemotherapy) accelerate bone turnover and the loss of bone mass.

Methods: In a randomized, double-blind, placebo-controlled study, 2 yrs of oral clodronate (a bisphosphonate) therapy significantly reduced the occurrence of bone metastases within the first 5 yrs in women with operable primary breast cancer. In a predefined subgroup of 555 patients, we examined the relationship between bone turnover response and incident bone metastases.

Results: At study entry, serum PINP (amino-terminal propeptide of type I collagen, a marker of bone turnover) was identical in both treatment groups. Median values were slightly higher in postmenopausal women than in premenopausal women (37.0 vs 34.5 µg/L, $P = 0.07$). During 2 yrs of therapy with clodronate, serum PINP values showed a median decrease of 26% while the placebo group had a median increase of 5% ($P<0.0001$ between groups). PINP levels in the clodronate group returned to baseline within 1 yr of stopping therapy. Using percentage changes between baseline and 1 yr, women were classified into responsive (>20% decrease in PINP), unchanged, or progressive (>20% increase in PINP) bone turnover groups. The percentage of women with a response was significantly higher (55% vs 31%) during clodronate therapy, while the number with progression was significantly lower (23% vs 41%)($P<0.0001$ both comparisons). In the clodronate group, the incidence of bone metastases was significantly lower in women with a response to therapy (4.8%) than in those with progressive bone turnover (17%, $P=0.016$). Median baseline PINP values were identical in women who later developed incident bone metastases (n = 56) and those who remained bone metastasis-free (n = 499) (35.0 µg/L both groups). At 1 yr, however, serum PINP values were significantly higher in women who subsequently developed bone metastases than in those remaining metastasis-free (median 40.0 vs 30.0 µg/L, $P = 0.003$). Similar results were noted if the analysis was based on percentage changes from baseline at 1 yr (median PINP % change +16.2% vs −12.0%, $P = 0.013$) or if women with known incident bone metastases at 1 yr were excluded ($P = 0.024$).

Conclusion: Clodronate plus standard adjuvant therapy in primary breast cancer is associated with reduced bone turnover and protection against bone metastases. Serum PINP has potential as a marker of response to therapy and possibly early detection of skeletal metastases.

353 Poster

Randomized pre-operative study of 750 mg of fulvestrant and 20 mg tamoxifen in premenopausal women with estrogen receptor-positive breast cancer

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Introduction: Fulvestrant is a pure antioestrogen that has been shown to be as effective as anastrozole in postmenopausal women with hormone receptor-positive breast cancer who have progressed or recurred on tamoxifen. A small pre-operative pilot study of fulvestrant at a dose of 250 mg showed no significant effect on breast cancers in premenopausal women. The aim of this study was to investigate the effects of fulvestrant (F) at a dose of 750 mg and compare its effects with tamoxifen (T) in a pre-operative study in premenopausal women.

Materials and Methods: 60 **premenopausal** women with operable, invasive estrogen receptor (ER)-positive breast cancer have been randomized to receive either:

- 750 mg of F (given as 3 separate intramuscular, 5 ml injections) or
- 20 mg of oral T both started 14–16 days before surgery.

Breast cancer tissue is being assessed before and after treatment for ER, progesterone receptor (PgR), HER2, and proliferation (Ki67) by immunohistochemistry with FISH for HER 2+. ER and PgR are given