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.

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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.

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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.

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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

as Allred scores and proliferation as % Ki67 positive cells. Results are presented as means (SEM); analysis is by paired t test.

Results: ER expression fell significantly with F from a mean Allred score of 7.15 (0.25) to 4.38 (0.61), $p < 0.0001$. The fall with T from 7.21 (0.19) to 4.14 (0.98) was also significant, $p < 0.0001$. The fall in ER was significantly greater for F than T, $p = 0.02$.

PgR expression fell significantly with F from a score of 6.11 (0.47) to 4.0 (0.63), $p = 0.002$. The change with T from 6.34 (0.31) to 5.39 (0.53) was not significant, $p = 0.06$. The fall in PgR was significantly greater for F than T, $p = 0.02$.

Proliferation F reduced the mean % of Ki 67 positive cells from 14.29 (1.55) to 8.18 (1.55), $p < 0.0001$, a 48% median reduction. T reduced proliferation from 12.36 (1.71) to 4.12 (0.98), a 71% median reduction, $p < 0.0001$. Direct comparison of F and T showed no significant difference, $p = 0.06$.

HER2: 5/25 F patients were HER 2+ as were 2/29 T patients. All these 7 patients had a reduction in tumour cell proliferation.

Average pain per injection was 1.6/10. Swelling (12%), bruising (16%), and skin sensitivity (12%) were also reported at injection sites with F. Side effects with T included light headedness (10%) and hot flushes (14%). With F hot flushes (16%), loose stools (12%) and headache (28) were reported. All were grade 1 or 2. No patient contacted staff due to adverse events, before routine review.

Conclusions: In premenopausal women 750 mg fulvestrant is well tolerated and significantly reduces ER and PgR expression to a greater degree than tamoxifen. Fulvestrant and tamoxifen both produce reductions in proliferation in ER+ breast cancers. Fulvestrant reduces proliferation in both HER2+ and Her2- tumors. Fulvestrant is biologically active in **premenopausal** women.

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Exemestane in adjuvant treatment of early breast cancer in postmenopausal women: results of a UK cost-effectiveness model

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Introduction: Standard endocrine adjuvant therapy for oestrogen positive, early breast cancer in postmenopausal women has been 5 years of tamoxifen. However, recent evidence from clinical trials shows that incorporating aromatase inhibitors into adjuvant therapy reduces recurrence rates. The Intergroup Exemestane Study (IES) has shown that switching women to exemestane, after 2 to 3 years of tamoxifen treatment, significantly improves disease free survival compared with continuing on tamoxifen. To fully evaluate the potential impact of exemestane from a policy perspective, the cost-effectiveness of switching to exemestane compared with continuing on tamoxifen has been evaluated.

Method: A decision (Markov) model was developed and adopted the UK health service perspective. The model simulates the disease progression and treatment pathway of early breast cancer over the lifetime of a female cohort. Adjuvant therapy is assumed to stop after 5 years and the model simulates the transitions among the health states: no recurrence, local recurrence, contra-lateral recurrence, distant recurrence, in remission, death from breast cancer and death from other causes. The model also includes treatment related adverse events with osteoporosis, endometrial cancer and thrombo-embolism incorporated into the model as separate health states. The main outcome measure is an incremental cost per quality-adjusted life year (QALYs) gained.

Results: Outcome analysis revealed an incremental advantage of exemestane over tamoxifen of 0.33 QALYs (13.24 v 12.91) and 0.44 (12.73 v 12.29) disease-free years. The mean total costs from the model are £7339 for exemestane and £5079 for tamoxifen treated patients. This results in an incremental cost per QALY of £6817. A probabilistic sensitivity analysis assessing the impact of variation around the key parameters was performed. This revealed that the incremental cost per QALY was less than £20,000 in 96.1% of 1000 simulations, giving confidence to our conclusion that adjuvant endocrine therapy with the switch strategy using exemestane is cost-effective.

Conclusion: Treatment with exemestane is more expensive than tamoxifen, although clinically important health gains are produced. Our model results show that switching postmenopausal women with early breast cancer to exemestane after 2 to 3 tears tamoxifen is a cost-effective alternative, compared with remaining on tamoxifen for 5 years for adjuvant treatment of early breast cancer. In the future, it is anticipated that this model could be useful to policy makers in other European countries facing decisions about exemestane and other new adjuvant therapies in this area of breast cancer.

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Neoadjuvant capecitabine chemoradiation (X-RT) for patients (pts) with locally advanced breast cancer (LABC) failing anthracycline-based neoadjuvant therapy: findings from a prospective phase II trial

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Background:, LABC remains a serious heath problem in Brazil, it represents approximately 30% of all newly diagnosed breast cancer pts. Anthracycline-based neoadjuvant therapy is a standard treatment, but approximately 30% of pts do not respond. For these refractory pts, there is no standard approach. Retrospective data from our institution indicate that, despite receiving RT, the majority of pts still progress: only 60% became operable and the majority of pts still have gross residual disease; 4 pts have minimal residual disease (9%) and only one pathologic complete response (pCR, 4%). X is highly active and well tolerated as a single agent and extends survival, time to progression and response rates when added to docetaxel in metastatic breast cancer. Because X is a potent radiosensitizer, and it has been proven effective and well tolerated in chemoradiation for locally advanced rectal cancer, we studied the concomitant use of RT and X in pts with LABC.

Materials and Methods: Eligible pts had inoperable LABC refractory to FAC, ECOG PS 0–2 and adequate bone marrow, renal and hepatic functions. Pts received RT 50cGy/d plus X 850 mg/m^2 bid orally on d1–14 for 2 cycles. Pts underwent surgery, if appropriate, after completion of neoadjuvant therapy. Pts with hormone receptor-positive tumors received tamoxifen after surgery.

Results: We enrolled a total of 30 pts. Baseline characteristics were as follows: median age 47 years (range 26–70); median tumor size (after anthracyclines) 80 cm* (range 36–357 cm*); inflammatory carcinoma (21%); hormone receptor positive tumor (ER 37.5%, PR 41%): 12 pts were HER2 2+ or 3+ (50%). Two pts were excluded from the analysis as they were protocol violators. Treatment with X-RT rendered 23 of the 28 evaluable pts (82%) operable. Four pts did not undergo surgery because of disease progression. After surgery, histology reports showed pCR in 3 pts (11%) and minimal residual disease in 4 pts (14%). A median residual tumor size of 11 cm* (range 0–72 cm*) and a median number of positive nodes of 2 was observed. Treatment was well tolerated. The most common (all grade) adverse events were nauseas/emesis, diarrhea and mucosite There were no grade 3/4 adverse events.

Discussion: Our data indicate that neoadjuvant X-RT is feasible, well tolerated and effective in pts with LABC refractory to FAC, rendering pts eligible for surgery. These findings suggest that a randomized study should be performed to compare RT vs. X-RT.

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Pegfilgrastim alone or with ciprofloxin significantly reduces febrile neutropenia and hospitalization vs G-CSF alone in breast cancer patients receiving neoadjuvant chemotherapy with docetaxel/doxorubicin/cyclophosphamide (TAC)

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Background and Objective: The TAC regimen (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 on day1, q21) is frequently associated with neutropenia and neutropenia-related complications, which are the major reasons for dose delays and dose reductions. We assessed 3 consecutive patient cohorts in a prospective randomized phase 3 trial (GEPARTRIO). The objective of this analysis was to evaluate the benefits of different prophylactic growth factor regimens.

Methods: Eligible patients had T2-T4 stage primary breast cancer and were expected to receive 6–8 cycles of TAC. This analysis included data from the first 4 cycles only. Patients (n = 915) were placed into 3 sequential cohorts: granulocyte colony-stimulating factor (G-CSF; filgrastim or lenograstim) on days 5–10 (n = 385, 2086 cycles); pegfilgrastim 6 mg alone on day 2 (n = 311, 1631 cycles); and pegfilgrastim 6 mg on day 2 plus ciprofloxin (C) (n = 219, 1074 cycles). The chi-squared test was used for statistical comparisons.