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