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.

**Results:** Prophylactic treatment with pegfilgrastim alone or pegfilgrastim with C was associated with a lower incidence of febrile neutropenia, first cycle febrile neutropenia, hospitalization, and anti-infective use compared with daily G-CSF (see table). Pegfilgrastim alone or with C also showed a lower incidence of grade 3/4 stomatitis and diarrhea ($p < 0.05$) compared with daily G-CSF.

**Conclusion:** Pegfilgrastim alone or in combination with ciprofloxacin was a more effective treatment for prevention of neutropenia and its related complications than daily G-CSF in early stage breast cancer patients treated with TAC chemotherapy.

| | *Cohort A* G-CSF (n = 385) 2086 cycles | *Cohort B* pegfilgrastim (n = 311) 1631 cycles | *Cohort C* pegfilgrastim + ciprofloxin (n = 219) 1074 cycles | Statistical comparison |
|---|---|---|---|---|
| Patient incidence of FN | 17% | 6% | 5% | *** A vs B<br>*** A vs C<br>ns B vs C |
| Incidence of FN in the first cycle | 9% | 2% | 0% | *** A vs B<br>*** A vs C<br>* B vs C |
| Number of hospitalizations | 391 | 210 | 161 | *** A vs B<br>** A vs C<br>ns B vs C |
| Number of anti-infective[a] administrations | 88 | 44 | 25 | ** A vs B<br>** A vs C<br>ns B vs C |

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; ns: not significant; FN: febrile neutropenia.
[a]defined as antibiotic, virostatic, or antifungal medications

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**Amenorrhea as a prognostic factor in premenopausal endocrine responsive early breast cancer patients**

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**Objectives:** Amenorrhea (Am) seems to be a prognostic factor in early breast cancer (EBC), especially in endocrine responsive disease. Aim of our analysis was to evaluate prognostic value of Am in premenopausal patients (pts) treated for EBC at Institute of Oncology in Ljubljana from 1986 to 1998.

**Patients and Methods:** To assure complete menstrual data, only 204 premenopausal HR positive pts included into international prospective trials evaluating the role of adjuvant systemic therapy (ChT alone n = 120, ChT plus Tam n = 19, ChT plus goserelin n = 37, goserelin alone = 28) were reviewed. Median age was 45 (27–54) years, majority of tumors (53%) were classified as T2, of median grade (43%), half of pts had positive lymph nodes. Amenorrhea was defined as a cessation of menstruation for at least 2 years. Endocrine responsive disease was defined as ER and/or PR $\geqslant$ 10 fmol/mg protein in primary tumor. Kaplan-Maier method and log-rank test were used for statistical analyses.

**Results:** Amenorrhea occurred in 85% (174/204) of all pts (in 76% of pts on ChT +/− Tam and in all patients on goserelin, respectively). Pts with Am had significantly higher 5-year DFS compared to pts without Am (75% vs. 53%; $p = 0.0081$). Also in the group of pts with Am induced by ChT alone, higher 5-year DFS rates were observed (76% vs. 57%; $p = 0.06$). Recovery of menstruation after 2 years of goserelin treatment did not affect 5-year DFS rates significantly ($p = 0.44$). After adjusting for ChT and Tam Am still showed borderline significance for DFS ($p = 0.06$). In Cox multivariate analyses with tumor size, tumor grade, nodal status and Am included, only nodal status retained independent prognostic value.

**Conclusions:** In our cohort of endocrine responsive premenopausal EBC patients, treatment related amenorrhea showed a prognostic impact on DFS. Also when Am was achieved only by ChT, it had a favorable effect with a trend to better DFS. No significant difference in DFS according to recovery of menstruation after goserelin cessation was observed.

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**Cost-effectiveness of exemestane versus tamoxifen as adjuvant therapy for early-stage breast cancer after 2–3 years treatment with tamoxifen in Sweden**

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Breast cancer is the most common cancer in Swedish women, with about 7000 new cases annually. Aromatase inhibitors are rapidly becoming the cornerstone of hormonal treatment for advanced disease and are now also used as adjuvant treatment in early-stage disease. The Intergroup Exemestane Study (IES) trial was a double-blind, randomized controlled trial in which postmenopausal women who had received two to three years of tamoxifen therapy following primary treatment of early-stage breast cancer were randomized to either continue on tamoxifen therapy or be switched to exemestane therapy. The results showed a disease-free survival hazard ratio of exemestane relative to tamoxifen in IES of 0.69.

The objective of this study was to assess the cost-effectiveness of adjuvant treatment with exemestane versus tamoxifen for early-stage breast cancer after 2–3 years treatment with tamoxifen in Sweden, based on findings in the IES. A Markov-type state-transition model was developed to simulate consequences after the end of the clinical trial, and to integrate the trial data with external data on mortality, costs and quality of life specific for Swedish women. The model used a life-long time horizon and the primary clinical outcome measure was quality adjusted life-years (QALYs).

Locoregional and distant recurrences occurred in about 18% of the patients, while new contralateral cancer occurred in 1–2%. Treatment of cancer recurrences contributed most to the total cost, while the largest difference in cost between the exemestane and tamoxifen groups was incurred by the adjuvant hormone treatments. The cost per QALY gained was about €20,000 in the base case analysis without inclusion of consequences of coronary heart disease. Inclusion of these events increased the cost-effectiveness ratio to about €31,000 for the base case assumption. Exemestane treatment in early breast cancer may therefore be a cost-effective option compared with tamoxifen, depending on the long-term effect of tamoxifen on coronary heart disease.

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**Preoperative concomitant hormone-radiotherapy for locally advanced breast cancer: Long-term clinical results of the Montpellier feasibility study**

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**Purpose:** To evaluate, with a 6-year median follow-up our data concerning survival and locoregional control in a pilot study of locally advanced breast cancer after primary hormonoradiotherapy (HT-RT).

**Patients and Methods:** Between 1987 and 2002, 80 patients (33 stage IIA, 27 stage IIB, 16 stage IIIA, and 4 stage IIIB according to AJCC staging system 2002) were treated by tamoxifen 20 mg daily and preoperative radiotherapy (50 Gy to the breast and nodal areas). Tamoxifen was started the first day of radiotherapy and was delivered for 3 months (median 90 days, range 60–130) before surgery.

Before any treatment, all patients were clinically evaluated by a surgeon and an oncologist and were considered not suitable for a conservative surgery. In all cases, primary tumors were histologically proven and were positive for estrogen (RE) and/or progesterone receptors (RP).

After surgery, tamoxifen was continued for 5 years, or until disease progression. Fifteen patients (19%) received adjuvant anthracyclin-based chemotherapy. Only four patients stopped tamoxifen before 5 years for toxicities.

**Results:** The median age of the patients was 60 years (range, 32–80 years). Sixteen (20%) patients were premenopausal and received LHRH analogues with tamoxifen. Compliance to neoadjuvant treatment was excellent and all patients received the complete sequence of preoperative radiotherapy and tamoxifen. Overall clinical response rate was 75% (64 patients), including a complete response rate of 8% (6 patients). Mastectomy and axillary dissection were performed in 44 patients (with clinical residual mass larger than 3 cm or central tumors), and conservative treatment in 36 patients (22 of them achieved clinical complete response or