of oral GLA/day (total = 2.8 gms) in addition to primary tamoxifen. Clinical response (by UICC criteria) was compared with a matched control group on tamoxifen (T) alone (n = 47). Serial tumour core-cut biopsies were taken for immunohistochemical assessment of changes in oestrogen receptor (ER) expression during treatment.

**Results:** The T + GLA cases achieved significantly faster clinical response (objective response OR vs. static disease SD) than tamoxifen alone, evident as early as 6 weeks on treatment (p = 0.010). T + GLA cases with larger fall in ER at 6 week biopsy had significantly better early response than tamoxifen cases displaying similar degree of ER fall (OR vs. SD 6 wks p = 0.026; 3 mths p = 0.016). These findings suggest that GLA may enhance the therapeutic effects of tamoxifen-induced ER down-regulation to produce a superior clinical response.

**Conclusion:** Our results propose GLA as a useful adjunct to primary tamoxifen in endocrine sensitive breast cancer, mechanism of action which may involve modulation of ER. Continued follow-up will determine whether this faster initial response will translate into longer ultimate duration of control.

## 74 ORAL

### Breast cancer clinical trials with Faslodex – A new class of antioestrogen

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**Purpose:** To describe the phase III clinical development of 'Faslodex' (ICI 182,780), a novel steroidal 'pure' (non-agonist) antioestrogen. Faslodex has a unique pharmacological profile, with effects that include potent antitumour activity whilst having no partial agonist activity on the uterus.

**Methods:** In a phase II study in postmenopausal women (n = 19) with tamoxifen-resistant advanced breast cancer (ABC), 69% of women showed a benefit of 'Faslodex' treatment (partial response or disease stabilisation >6 months) 1 with a median duration of response of 25 months[2]. The phase III programme, currently in progress, includes two large randomised trials, each comparing the efficacy (time to progression; response rate; time to death) and safety of 'Faslodex' versus 'Arimidex' (anastrozole) 1 mg daily in postmenopausal women with ABC having failed previous hormonal treatment. Faslodex is given as a once-monthly i.m injection. Each study will recruit 600 patients. A multinational randomised double blind trial to compare the efficacy and safety of 'Faslodex' with tamoxifen as first-line treatment in postmenopausal women with ABC will be initiated in the near future.

**Conclusion:** Faslodex has shown good activity in phase II studies. The ongoing clinical programme will define the role of this new pure antioestrogen in the hormonal treatment of ABC. The current status of these trials will be presented.

'Faslodex' and 'Arimidex' are trademarks, the property of Zeneca Ltd

[1] Howell Lancet 1995; 345, 29.
[2] Robertson Breast 1997; 6: 186–189.

## 75 ORAL

### Combination of antimetastatic and antiproliferative therapies in the treatment of experimental breast cancer

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**Purpose:** High expression of different proteases involved in the metastatic process and neo-angiogenesis appears to be associated with poor clinical outcome. The aim of the present study was to evaluate the antitumor and antimetastatic effects of various protease inhibitors as single agents and in combination with doxorubicin (Dox).

**Methods:** As experimental model the transplantable rat breast adenocarcinoma (BN 472), that metastasizes to axillary lymph nodes and lungs of Brown Norway rats, was used. The animals were treated during 3 weeks with the metalloproteinase-inhibitor CGS27023A (kindly provided by Novartis), the uPA-inhibitor amiloride and the cytotoxic agent Dox.

**Results:** As single agents CGS 27023A, amiloride or Dox inhibited s.c. tumor growth with 50–60% as compared with controls ($p < 0.01$). Amiloride ($p < 0.05$) and CGS27023A ($p < 0.01$) added to the antitumor effect caused by Dox. Moreover, all treatments caused a significant decrease of lymph node weight (55–65% inhibition, all $p < 0.01$), and of the number of lung foci ($p < 0.01$). Regarding the number of lung foci, combination treatment of Dox + CGS27023A was more effective than either treatment by itself.

**Conclusion:** The addition of protease inhibitors to standard antiproliferative agents significantly improved the antitumor effects and decreased the development of metastases. Therefore such combination treatment might be of great value in clinical breast cancer.

## 76 ORAL

### Influence of amifostine (A) on the toxicity and pharmacokinetics (PK) of docetaxel (D) in breast cancer patients: An EORTC-IDBBC study

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D (100 mg/m$^2$) has been administered as 1$^{st}$ or 2$^{nd}$ line therapy for metastatic breast cancer combined with A (910 mg/m$^2$) from the second cycle onwards. PK of D have been performed during the first 2 cycles. Clinical data are available for 16 patients (pts) (55 cycles, median number of cycles per patient 4 (2–8) in pts off study and 2$^+$ (2–8)) for all pts. The regimen is very well tolerated with no toxicity related to A and no dose reductions needed. No difference in toxicties was observed between the first 2 cycles (–/+ A) but, in 39 cycles administered with A, the incidence of febrile neutropenia (3% of cycles), skin toxicity (6% of patients) and D related pleural effusion gr 2 (6% of patients) were lower than expected. PK preliminary results suggest that A does not influence D clearance but may interfere with the concentration peak of D. These results warrant a prospective randomized study of D ± A in order to further delineate the potential chemoprotective role of A on D.

## 77 ORAL

### EORTC 10968; Phase I study of Caelyx™ at a six week interval in patients with metastatic breast cancer

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**Rationale:** Caelyx is pegylated liposomal doxorubicin (formerly known as Doxil). It differs from doxorubicin in terms of its prolonged $t_{1/2}$ (>50 hours) and its tendency to accumulate in skin and mucous membranes. Earlier studies at q3W and q4W intervals have demonstrated palmar-plantar erythrodysesthesia as a major toxicity.

**Methods:** Patients ≥ 70 yo received Caelyx as first line (adj anthracycline mandatory) or second line (no anthracycline for MBC) therapy for MBC. Patients ≥ 70 yo received Caelyx as first or second line therapy for MBC (no prior anthracycline). Caelyx was administered as a 1 hour IV infusion q6W. Neither 5HT antagonists nor steroids were prescribed. Prophylactic mouthwashes were given routinely.

**Results:** 14 patients have been treated to date (median age 68 (43–78)). *60 mg/m$^2$*: 8 patients have been treated, 4 of whom have received ≥2 cycles. One DLT has been reported (G3 stomatitis), but toxicity is otherwise mild. One PR has been observed. *70 mg/m$^2$*: 6 patients have been treated, none of whom has yet received ≥2 cycles. No significant skin or haematological toxicity, alopecia or nausea/vomiting has been noted. Stomatitis is the only significant toxicity and may be dose limiting. One PR has been observed.

Final results will be presented.

## 78 POSTER

### Plasma thrombospondin (pTSP) in early and advanced breast cancer

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**Purpose:** TSP has been shown to promote metastasis in animal models by increasing adhesion of cancer cells to endothelial cells. We hypothesized that increased production of TSP by breast cancer would be associated with metastases

**Methods:** TSP was measured in the plasma of women with early breast cancer (EBC) (n = 53), advanced breast cancer (ABC) (n = 60), women who had undergone surgery for breast cancer with no evidence of recurrent

disease (n = 49), normal premenopausal (at 8 equal intervals across the menstrual cycle) (n = 8) and postmenopausal women (n = 28). Levels were measured by radio-immunoassay.

**Results:** pTSP in women with EBC (median 461, IQR = 346–844) was elevated when compared to women following surgery (median = 227, IQR = 177–270) ($p < 0.001$), and normal controls (median = 225, IQR = 188–260). Women with EBC who had nodal metastases (n = 22) had higher levels of TSP (median 509, IQR = 411–997) than women who were node negative (median = 297, IQR = 225–401) (n = 31) ($p < 0.05$). pTSP in women with high grade tumours (n = 36) was raised when compared to grade 1 tumors ($p < 0.05$). pTSP levels in women with ABC (median 588, IQR = 401–904) were higher than women with no evidence of recurrent disease ($p < 0.001$) and normal controls ($p < 0.001$).

**Conclusion:** Plasma thrombospondin levels are a marker of metastatic disease in EBC and ABC and may be useful in assessing response to chemotherapy.

## 79 POSTER

### The 'ZEBRA' study: An open randomised trial of 'zoladex' vs CMF as adjuvant therapy in the management of node positive stage II breast cancer in pre/peri-menopausal women aged 50 years or less

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To evaluate long-term use of Zoladex (Z), an LHRH agonist, as an adjuvant treatment for breast cancer in pre/perimenopausal women, this study was designed using cytotoxic chemotherapy, the current systemic adjuvant treatment of choice, as a comparator. Recruitment started in 1990 and closed in December 1996. 1640 patients from 102 centres in Europe, Australia and Argentina, were randomised to Z (2 years therapy – 3.6 mg s/c depot every 28 days) or CMF (cyclophosphamide, methotrexate, 5-fluorouracil; 6 cycles; 4 weekly). The aims are to compare disease-free survival, overall survival, safety, adverse reactions and quality of life. As a sub-protocol (n = 187), the effect of treatment on Bone Mineral Density was assessed. Oestrogen receptor status is currently negative for approx. 20% – review ongoing. Data collection is continuing but preliminary review of demographic data shows: breast conserving surgery was carried out in 47% patients, mastectomy in 53% and radiotherapy was given in 69%. 70% of the patients had 1–3 positive nodes and 47% had a tumour size ≤2 cm. Demographic and pre-treatment characteristics were comparable in the two arms. First analyses are planned to be reported mid-1999.

['Zoladex' (goserelin) is a trademark property of Zeneca Limited.]

## 80 POSTER

### First interim results of an ongoing study comparing the GNRH-agonist leuprorelinacetate and CMF as adjuvant treatment in premenopausal breast cancer

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**Purpose:** Chemotherapy is considered the best option in daily practice for adjuvant treatment of node-positive premenopausal breast cancer patients. Irreversible hormonal ablation by bilateral oophorectomy is an alternative which is not acceptable for the majority of patients. The ongoing TABLE Study compares a standard CMF-polychemotherapy with two years of treatment with the GNRHa leuprorelinacetate 3-month-depot (LAD 3 M) in terms of efficacy, safety and endocrinological effects.

**Methods:** Prospective, randomized, open multicentre clinical phase III trial, for node positive ($N_{1-9}$), $E_3$-receptor-positive patients.

| Parameter | CMF, n = 75 | LAD 3 M, n = 77 |
|---|---|---|
| Age, years (Mean ± SD) | 42.3 ± 3.5 | 40.4 ± 4.3 |
| $T_1/T_2/T_3$ (%) | 42/28/30 | 44/25/31 |
| $N_{1-3}/N_{49}$ (%) | 55/45 | 52/48 |
| ER+/PR+ (%) | 96/63 | 97/69 |
| Safety | CMF, N = 213 | LAD 3 M, n = 207 |
| Serious Adverse Drug Reactions (ADR, n) | 5 | 0 |
| Withdrawals due to ADRs | 3 | 2 |

**Results:** Since 1995 420/600 patients have been already enrolled. The baseline parameters and the first safety results of 152 patients analyzed are presented in the table.

Almost all patients treated with LAD 3 M showed a sustained suppression of oestradiol levels beyond castration range (≤30 pg/ml). In contrast, most of the patients treated with CMF have signs of residual ovarian activity or nearly normal oestradiol levels after cessation of the chemotherapy.

**Conclusions:** LAD 3 M and CMF have different safety profiles and lead to distinct endocrine situations. A long-term follow-up is necessary to assess the impact of the two treatment regimens on recurrence rates and time to tumor progression. In addition the tolerability of LAD 3 M and CMF will be important issues which could have a major impact on patients' acceptance and quality of life.

## 81 POSTER

### Effect of dietary GLA +/– tamoxifen on growth and ER in a human breast cancer xenograft model

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**Purpose:** Gamma Linolenic Acid (GLA) has been identified to possess a number of selective anti-tumour properties including modulation of steroid receptor structure and function. The present study has investigated the effect of dietary GLA on the growth rate and oestrogen receptor (ER) expression of ER+ve human breast cancer in a rodent xenograft model.

**Methods:** Experimental diets A, B, C, D were commenced after subcutaneous innoculation of 40 female nude mice with the MCF-7 BIM cell line (Group A = control diet: B = GLA supplement: C = control diet + s.c. tamoxifen pellet: D = GLA + tamoxifen pellet; 10 mice/group). The mice were terminated when tumour cross-sectional area reached 250 $mm^2$. ER H-score was assessed from immunohistochemical assay of frozen tumour samples.

**Results:** All mice remained healthy on the diets. Groups C and D had significantly slower tumour growth ($p = .0002$, $p = .0006$) with similar trend in B ($p = .065$) compared to control group A. ER was significantly reduced in all groups compared to A ($p = .00001$ overall) with group D displaying greater degree of reduction than with either therapy alone (B vs D $p = .0002$; C vs D $p = .0002$).

**Conclusions:** This xenograft model has demonstrated GLA to have a modulatory effect on expression of ER and suggests this may be a mechanism by which GLA inhibits ER +ve breast cancer growth. The effects of GLA on ER function and the possibility of synergistic action with tamoxifen via down-regulation of ER require further investigation.

## 82 POSTER

### Prognostic value of cathepsin D expression and association with histomorphological subtypes in breast cancer

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**Purpose:** Additional prognostic factors are of great importance in breast cancer patients in order to tailor adjuvant therapy. The present study investigates the prognostic value of invasive ductal carcinomas of the breast.

**Methods:** Cathepsin D expression was detected immunohistochemically in 103 breast cancer patients stage pT1/2. We assessed the association between cathepsin D expression and histomorphological tumour subtypes (invasive ductal carcinoma with extensive intraductal component, multifocal tumour). Cathepsin D expression was examined at two cut-off levels (positive/high immunostaining score) and separately identified within the epithelial and stromal component of all tumours.

**Results:** Epithelial expression was detected in 32/20 patients (31.1%/19.4%). Stromal component expressed cathepsin D in 35/19 cases (34%/18.4%). Epithelial cathepsin D expression was associated with stage (P = 0.02/0.02) and nuclear grade (P = 0.0.03/0.02), but not with lymph node or oestrogen receptor status. Epithelial cathepsin D expression showed significant prognostic value for overall survival (log-rank P = 0.003/0.01) and recurrence-free interval (log-rank P = 0.04/0.02). Cathepsin D expression in stromal cells was associated with neither established prognostic factors nor survival. Multivariate analysis revealed that cathepsin D expression failed to be an independent predictor of patient's outcome. Cathepsin D expression shows no significant association with histomorphological subtypes of breast cancer.