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 1st or 2nd 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