0.001). There were 2 toxic deaths in the AT arm (1 patient septic). Efficacy results were analysed on intent to treat basis. All responses were subjected to blinded review by the principal investigator.

Conclusion: In this phase III study, AT produced a significantly higher objective response rate than FAC. When clinical benefit was considered the difference remained significant. Median progression-free survival was equal in both arms. Data on overall survival are under analysis and will be presented.

672 ORAL

Randomised phase II trial (M77001) of trastuzumab (Herceptin®) plus docetaxel versus docetaxel alone, as first-line therapy in patients with HER2-positive metastatic breast cancer

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Background: Herceptin administered intravenously (iv) weekly in combination with chemotherapy has been shown to increase survival in women with HER2-positive metastatic breast cancer (MBC). Herceptin is currently licensed for use in combination with paclitaxel and as monotherapy. The taxanes paclitaxel and docetaxel are commonly used in the treatment of patients with MBC. Preclinical data suggest that Herceptin in combination with docetaxel may be as, or even more effective, than Herceptin and paclitaxel. Several small clinical studies have demonstrated good response rates for the combination of Herceptin and docetaxel. Therefore, this promising combination has been investigated in a randomised trial.

Patients and Methods: HER2 testing was performed locally or in a reference laboratory using immunohistochemistry (IHC) or fluorescence *in situ* hybridisation (FISH). Patients (pts) with IHC 3+ or FISH-positive disease (IHC 2+ was allowed at the beginning of the study), and at least one measurable lesion, were eligible. Pts with HER2-positive MBC were randomised to receive Herceptin (4 mg/kg iv loading dose followed by 2 mg/kg weekly until disease progression) in combination with docetaxel (100 mg/m^2 iv every 3 weeks x 6 cycles) or docetaxel alone. Pts on docetaxel monotherapy were allowed to crossover to receive Herceptin on disease progression. Tumour response was assessed according to WHO criteria by the investigator and by an independent radiological review board.

Results: 188 pts were recruited between April 2000 and October 2002; recruitment is complete. 94 pts were randomised to receive Herceptin plus docetaxel, and 94 pts to receive docetaxel alone. Preliminary safety data indicate that Herceptin plus docetaxel was generally well tolerated, with no unexpected toxicities seen to date. The incidence of febrile neutropenia/neutropenic sepsis was 19% (18/94 pts) in the Herceptin plus docetaxel arm versus 16% (15/94 pts) in the docetaxel-alone arm. Two pts died due to septicaemia in the docetaxel-alone arm. Minor asymptomatic falls in left ventricular ejection fraction of uncertain significance were common in this study but only one patient (treated with Herceptin plus docetaxel) developed congestive heart failure (CHF). This patient had received prior adjuvant doxorubicin (cumulative dose 300 mg/m^2) and developed CHF about 5 months after starting Herceptin and docetaxel.

Conclusions: The observed rate of CHF of about 1% to date in M77001 compares favourably with that observed for Herceptin plus paclitaxel. No unexpected toxicities have been seen to date. Results of the primary efficacy analysis will be presented.

673 ORAL

Shorter survival times following adjuvant endocrine therapy in oestrogen (ER) - and progesterone receptor (PgR) positive breast cancer (BC) overexpressing c-erbB-2 or with an increased expression of vascular endothelial growth factor (VEGF)

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Background: Expression of oestrogen- (ER) and progesterone receptors (PgR) is predictive factors for benefit from endocrine therapy. Overexpression of c-erbB-2 and high VEGF have been associated with a worse outcome in retrospective studies, including patients receiving adjuvant endocrine therapy. The worse prognosis seen after endocrine therapy has been claimed to partly be explained by the correlation between high c-erbB-2 and VEGF expression and steroid receptor negativity, and the prognostic value of these factors have in some studies wanished when ER negative patients have been excluded.

Aims: To investigate the possible prognostic value of c-erbB-2 and VEGF in 679 patients with primary breast cancer, including the group of 388 receiving adjuvant endocrine therapy.

Materials and methods: Patients with a diagnosis of breast cancer from 1993 to 1996 at the Karolinska Hospital and St Görans Hospital, Stockholm with cytosols after determination of steroid receptors were included (n=679). Of these, 423 had a node-negative BC, 200 a node-positive BC, in 56 patients was axillary disection not performed. The median age was 64 years (range 33 to 89), and the median follow-up time was 94 months. Adjuvant therapy was given to 573 patients; endocrine mostly tamoxifen +/- radiotherapy (RT) (n=388), only RT (n=98), or chemotherapy +/- RT +/- endocrine therapy (n=87). VEGF and c-erbB-2 status were determined by enzyme immuno-sorbent assays (ELISA). In 200 patients, c-erbB-2 status was also determined by immunohistochemistry (IHC) with the monoclonal antibody CB11.

Results: Overexpression (+3) of c-erbB-2 by IHC was found in 12% of the tumours. Correspondingly the 12% with the highest c-erbB-2 values by the ELISA were classified as overexpressers. Overexpression of c-erbB-2 was associated to higher VEGF content (p=0.004). Both c-erbB-2 (RFS p=0.03344, OS p=0.02176) and VEGF (RFS p=0.00779, OS p=0.00187) were significantly related with shorter survival in the total population. Other factors correlated with survival were tumour size (RFS p<0.0001, OS p<0.0001), nodal status (RFS p<0.0001, OS p<0.0001), ER- (RFS, p=0.00150, OS p=0.02792), PgR (RFS p=0.00779, OS p=0.00875), and menopausal status for OS (p=0.00050), but not for (RFS p=0.99119). Patients with high VEGF or c-erbB-2 positive BC receiving adjuvant endocrine therapy (n=388) had significantly shorter survival; c-erbB-2 (RFS p=0.01259, OS p=0.02162), VEGF (RFS p=0.01545, OS p=0.00482). The results remained when only ER and PgR positive patients were included in survival analyses (n=317); c-erbB-2 (RFS p=0.00713, OS p=0.00268), VEGF (RFS p=0.01363 OS p=0.00570) respectively.

Conclusion: Overexpression of c-erbB-2 or higher VEGF expression adds in this retrospective analysis information concerning patients outcome after adjuvant endocrine therapy in ER and PgR positive BC. Results from multivariate analysis will be presented.

674 ORAL

Topoisomerase II alpha (TOP2A) alterations as a predictive marker for epirubicin sensitivity in 805 high-risk breast cancer patients. A randomised DBCG Trial (DBCG89D).

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Background: The purpose of this study was to evaluate *TOP2A* as predictive marker for the efficacy of epirubicin in the adjuvant setting of breast cancer patients. Inhibition of topoisomerase IIα is the primary cytotoxic action of the anthracyclines and it is hypothesised, that copy number changes of the *TOP2A* gene would lead to an altered sensitivity to treatment with epirubicin.

Material and methods: Nine-hundred-and-sixty-two pre- and postmenopausal high-risk patients were enrolled in the protocol DBCG 89D between January 1990 and November 1999. The patients were randomly allocated to either 9 x CMF (cyclophosphamide 600 mg/m^2, metrotrexate 40 mg/m^2 and 5-flurouracil 600 mg/m^2) every 3 weeks (n=495) or 9 x CEF (cyclophosphamide 600 mg/m^2, 5-flurouracil 600 mg/m^2 and 60 mg/m^2 epirubicin) (n=467). Paraffin-embedded tumour-tissue was available from

84% of the patients. The patients were screened for HER2 overexpression by the HercepTest™ and were analysed for *TOP2A* abnormalities with the *TOP2A* FISH pharmDx™ (DakoCytomation, Glostrup). Cases were scored as *TOP2A* amplified when the ratio of *TOP2A* gene signals and centromere 17 control signals was * 2. A deletion was scored when the ratio was < 0.8. Recurrence-free survival (RFS) was used as end-point and was defined as the period from enrolment to relapse (local or distant)

Results: So far *TOP2A* gene copy changes have been evaluated in all 307 tumours known to be HER2 2+ or 3+ positive and in 105 tumours known to be HER2 0 or 1+ positive. *TOP2A* amplification or deletion was found in 37% of the patients analysed so far. When adjusted for classical prognosticators, we found that patients with *TOP2A* alterations had a reduced relative risk of recurrence if treated with CEF (HR = 0.42; CI: 0.27-0.66). This in contrast to patients with a normal *TOP2A* genotype for whom similar outcome was observed in the CMF and CEF treated groups, (RFS: HR = 1.01; CI: 0.68-1.49).

Conclusion: *TOP2A* gene copy number changes seem to predict a favourable effect of adjuvant epirubicin therapy in primary breast cancer. *TOP2A* changes were not restricted to HER2 altered tumours and the *TOP2A* analysis will be completed on all tumours.

675 ORAL

Anastrozole is an effective neoadjuvant therapy for patients with hormone-dependent, locally-advanced breast cancer irrespective of cerbB2 status

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Background: the efficacy and safety of anastrozole 1 mg once daily as neoadjuvant therapy in postmenopausal women with locally-advanced breast cancer (LABC) was investigated in an open-label trial.

Methods: 112 patients were included in the trial; patients had histopathologically-confirmed unilateral, oestrogen receptor-positive LABC (stage IIIA/B). After 3 months of neoadjuvant treatment with anastrozole, clinical responses were evaluated. All patients with a complete or partial clinical response (cCR or cPR) underwent surgery (radical modified mastectomy), then continued on 1 mg anastrozole as adjuvant therapy for 2 years or until progression. Primary end point was objective response (cCR+cPR) rate, secondary endpoints included pathological complete or partial response (pCR or pPR) rate. CerbB2 and Ki67 analysis was carried out on all tumours using the histopathological blocks taken at the time of first diagnosis.

Results: tumour response rates for all patients and according to cerbB2 and Ki67 status are presented in the table.

Tumour response	All patients (%)	cerbB2 status (%)		Ki67 status (%)	
		Negative	Positive	<10%	*10%
	n=112	n=79	n=33	n=61	n=51
Clinical response					
cCR	54.5	60.8	39.4	63.9	43.1
cPR	28.6	34.2	15.2	32.8	23.5
No clinical response	17.0	5.1	45.5	3.3	33.3
Objective response					
(cCR+cPR)	83.0	94.9	54.5	96.7	66.7
Pathological response					
pCR	16.1	21.5	3.0	23.0	7.8
pPR	67.0	73.4	51.5	73.8	58.8
No pathological response	17.0	5.1	45.5	3.3	33.3

Conclusions: the response rates following neoadjuvant anastrozole indicate that it is highly effective in postmenopausal women with hormone-dependent LABC, regardless of cerbB2 or Ki67 status. Further follow-up is required to determine the impact of anastrozole on disease-free, and overall, survival following surgery in these patients.

676 ORAL

An assessment of fracture rates over time (between 6 and 48 months) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial

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Background: Anastrozole (1 mg once daily [od]) has shown efficacy benefits compared with tamoxifen (20 mg od) for treatment of postmenopausal women with early breast cancer (EBC). An overall assessment of safety data showed a benefit for anastrozole, although incidence of fractures was significantly greater with anastrozole compared with tamoxifen.

Methods: Fracture incidence from the ATAC study was assessed every 6 months up to 48 months of treatment; differences in patterns of time-to-fracture for anastrozole versus tamoxifen were assessed.

Results: At the first analysis (median duration of therapy 31 months), fracture incidence was 5.9 vs 3.7% for anastrozole and tamoxifen, respectively (relative risk [RR] anastrozole/tamoxifen 1.59). Data from a safety update (median duration of therapy 37 months) indicated that risk of fractures did not worsen over time (fracture incidence was 7.1 vs 4.4% for anastrozole vs tamoxifen, respectively; RR 1.60, 95% confidence interval 1.301.97, p<0.0001).

Time (months)	6-monthly fracture rates/100 patients		Anastrozole/tamoxifen 6-month hazard ratio
	Anastrozole (n=3092)	Tamoxifen (n=3093)	
6	1.11	0.99	1.14
12	0.93	0.58	1.61
18	1.36	0.69	1.98
24	1.57	0.61	2.57
30	1.39	0.96	1.45
36	1.09	0.66	1.66
42	1.50	1.37	1.09
48	1.07	0.80	1.34

Fracture rates (see table), remained fairly constant for both anastrozole (range 0.93 to 1.57) and tamoxifen (0.58–1.37), with the 6-monthly fracture rates for anastrozole plateauing after 24 months. The maximum differences between anastrozole and tamoxifen were seen at 18 and 24 months. Similar patterns were seen for osteoporotic fractures' (hip + spine + wrist).

Conclusions: anastrozole leads to an increased fracture incidence compared with tamoxifen, a drug known to have a positive effect on bone mineral density. Importantly, the fracture rate in the anastrozole-treated group appears to stabilise after peaking at 2 years. Although differences in fracture rates exist, the overall benefit to risk in EBC remains unchanged, favouring anastrozole.

Head and neck cancer

677 ORAL

Results of a phase II study of cetuximab in combination with carboplatin in patients (pts) with recurrent or metastatic nasopharyngeal carcinoma (R&M NPC) who failed to a platinum-based chemotherapy

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Background: Recurrent or metastatic NPC pts usually respond well to palliative platinum-based chemotherapy, indeed for a short period. Relapsing or non-responding patients have few valid therapeutic options, if any. Since studies have revealed a high expression rate of epidermal growth factor receptor (EGFR)- up to 94% in NPC pts with its prognostic significance, cetuximab (Erbitux®), a chimeric anti-EGFR monoclonal antibody, has been evaluated in R&M NPC pts.

Design: a multi-center, single arm phase II study in R&M NPC pts with measurable disease and disease progression on or within 12 months after end of a platinum-based chemotherapy. Experimental therapy: cetuximab (Erbitux™) 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly plus carboplatin AUC 5 administered every 3 weeks.