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