N = 359 had received Tamoxifen (TAM) alone, N = 181 received chemotherapy (CHEM) alone, N = 300 received CHEM + TAM, and N = 270 received no adjuvant therapy (NO RX). There were significant differences in the mean age of each group, with the TAM group being the oldest (mean 62.5 yrs) and the CHEM group being the youngest (mean 46.7 yrs). Both age and time since diagnosis were controlled for in all statistical analyses. We found no significant differences in global QOL, mental health score, fatigue, or depression among the four BCS groups. The NO RX group had an MOS SF-36 Physical Functioning Composite Score that was at the median for a normal healthy population, while those in the adjuvant treatment groups scored slightly but significantly lower ($P = 0.02$). The MOS SF-36 Mental Health Composite Score was not significantly different among the groups and approximated the normal population. Current sexual functioning was significantly worse for patients who had received any CHEM ($P = 0.0001$) compared to NO RX. Hot flashes, night sweats, and vaginal discharge were reported more often in BCS on TAM ($P = 0.0001$). Vaginal dryness and pain with intercourse were reported significantly more often in BCS treated with CHEM. Overall, BCS function at a high level, similar to healthy women without cancer. However, compared to BCS with NO RX, those who received CHEM have significantly more sexual problems, and those treated with TAM experience more vasomotor symptoms.

Saturday, February 28, 1998 **8.15–10.00)**

Session 11 Clinical Research Around the World: Review of Trials of Cooperative Groups

S40 North American adjuvant breast cancer trials

J.S. Abrams. *National Cancer Institute, Bethesda, MD, USA*

The National Cancer Institutes in the U.S. and Canada sponsor Cooperative Groups to perform randomized trials in distinct subsets of early breast cancer. For women with ductal carcinoma in situ (DCIS), two trials (ECOG-5194 and RTOG-1026) are evaluating adjuvant breast irradiation (RT) in women with "good risk" lesions. NSABP trial (B-21) tests whether adjuvant breast RT, tamoxifen or both are needed for women undergoing lumpectomy for invasive tumors ≤ 1 cm. In node (−), receptor (+), invasive tumors, two trials are evaluating whether the somatostatin analog, octreotide, can add to tamoxifen (NSABP B-29 and MA-14). For women at higher risk of relapse, the focus has been on improving chemotherapy. The roles of dose intensity and dose density have been evaluated at dose levels requiring either G-CSF or stem cells. INT-0137 has tested concurrent doxorubicin/cyclophosphamide (AC) versus the same drugs administered sequentially at maximal doses with G-CSF. NSABP B-25 increased doses of C (up to 2400 mg/m^2) and INT-0148 escalated doses of A (up to 90 mg/m^2) compared to standard doses of the AC regimen. CALGB 9082 randomized patients with ≥ 10 (+) nodes to high dose chemotherapy with stem cell support vs. the same drugs at lower doses with G-CSF. The introduction of taxanes into adjuvant regimens has been a major area of investigation. Following AC, patients have been randomized to paclitaxel or no further therapy in INT-0148 and NSABP B-28 and to docetaxel in NSABP B-27. With the introduction of taxanes, dose density is being reevaluated in a trial (CALGB-9741) that compares AC followed by paclitaxel (T) to the three drugs given sequentially with both regimens given either every 2 or 3 weeks. For women with 4–9 nodes, sequential A-T-C with G-CSF is being compared to AC × 4 followed by high dose chemotherapy with stem cell support. Two studies are targeted to women <65–70 y.o. INT-0151 tests whether fenretinide can add to tamoxifen in women with node (+), receptor positive disease and CALGB-9343 studies whether breast RT can be safely omitted from conservative therapy in tumors <2 cm. when tamoxifen is given.

S41 Clinical research around the world: IBCSG trials

A. Coates. *IBCSG Scientific Advisory Committee, University of Sydney and Royal Prince Alfred Hospital, Sydney, Australia*

The International Breast Cancer Study Group (IBCSG) was established in 1977 as the Ludwig Breast Cancer Study Group. It involved member institutions from Switzerland, Australia, New Zealand, Sweden, Italy, Slovenia, South Africa, Spain, Canada, Hong Kong and at various times from other countries. It has completed seven trials in three generations, and has a further 8 trials currently open. Total accrual exceeds 11,000, and more than 8000 patients are in active follow up.

Early trials established the pattern of addressing important biological questions, and adapting the randomisation to the risk group of the patient. The first two generations of trials demonstrated that combined modality chemoendocrine therapy was superior to endocrine therapy alone or no therapy in node-positive postmenopausal patients; that a single peri-operative cycle improved disease-free survival in node negative patients, but was inferior to more prolonged therapy in node-positive patients, and that six conventionally-timed cycles of CMF were as effective as seven cycles commenced in the peri-operative period.

Recently reported trials in node-positive patients showed that three early cycles of CMF chemotherapy added to tamoxifen in postmenopausal patients, while late reintroduction of chemotherapy appeared detrimental, particularly in patients with ER-negative tumours. In premenopausal patients six initial cycles was superior to three, especially in younger patients.

Current studies in node-positive patients are addressing the role of a gap between courses of different chemotherapy, and the relative value of the antioestrogens tamoxifen and toremifene. In node-negative, premenopausal patients ovarian suppression with goserelin is being tested either instead of or added to CMF, while the value of initial CMF before tamoxifen is being tested in node-negative postmenopausal patients. For high risk patients a triple-transient regimen is being compared with conventional dose therapy.

Planning for future trials recognises the need for rapid accrual of large numbers of similar patients, and therefore the need for Inter-Group collaboration. The emergence of the Breast International Group as a consortium of European, Australasian and Canadian cooperative Groups is important to the rapid evaluation of new agents and strategies.

S42 Scandinavian/nordic adjuvant trials in breast cancer

H.T. Mouridsen. *Copenhagen University Hospital, Denmark*

The scandinavian breast group (SBG) was established 1989 with members from Denmark, Norway, Sweden, Finland and Iceland representing surgery, histopathology, oncology, statistics and basic research.

In 1993 SBG analysed all ongoing adjuvant studies in the nordic countries. It appeared that 20 protocols were ongoing, analysing 7 major questions. The individual trials only occasionally recruited sufficient number of patients to enable valid conclusions within a reasonable time.

As a result of this analysis a Clinical Trials Committee was established, the objective being to coordinate trials in primary and advanced disease.

Recently closed trials include:

(1) Post, node pos, rec pos/unknown. TAM 1 yr vs TAM 2 yr (DK, Iceland) (N = 1750)
(2) Post, node pos + neg. TAM 2 yrs vs TAM 5 yrs (Sweden) (N = 3545)
As a result standard adjuvant endocrine therapy is now TAM, 5 yrs.
So far standard adjuvant chemotherapy is CMF.

Trials ongoing for the moment include (N indicate number of patients randomized Oct. 1997).

(1) Pre, node pos, rec pos: castration vs CMF (N = 700)
(2) Pre and post, high risk, rec neg and pre node neg, grade II–III: CMF vs CEF ± pamidronate (N = 1150)
(3) High risk ≥ 8 pos nodes or ≥ 5 nodes, rec neg, and grade II–III or high s-phase. High dose chemotherapy + stemcell transplantation vs dose escalating therapy (N = 460)

According to present criteria of entry to adjuvant studies the theoretical annual numbers of patients in the nordic countries eligible for adjuvant studies with chemotherapy is 1000 and for endocrine therapy 1500. However, a substantial proportion of patients do not accept to be randomized and huge numbers are required in future adjuvant studies. Therefore SBG is keen to establish international collaboration.

S43 EORTC and big trials

M.J. Piccart, L. Biganzoli, A. Goldhirsch. *Breast International Group,*

The overview has been a remarkable undertaking in trying to shed some light in the darkness of our Breast Cancer (Br CA) adjuvant clinical trials: it has indeed provided us with a considerable enrichment in our understanding of the disease and of its interactions with current adjuvant treatment modalities. However, the overview probably represents a "treatment" for the "suboptimal health" of our current clinical research and this treatment has its own limits.

A European Intergroup called BIG has therefore been set up with the hope to give an exponential growth to European research in the adjuvant treatment of Br CA and to stimulate collaboration with the already existing American Intergroup.

Priorities for the coming years include a) support to: 1) a Scandinavian Trial looking at the issue of Hormonal Replacement Therapy 2) an EORTC trial looking at the potential anti-angiogenic and anti-invasion effects of a new anti-oestrogen given at the time of surgical biopsy 3) an IBCSG trial looking at biphosphonates given at the time of loco-regional relapse 4) an EORTC initiative to focus on the issue of fertility in very young Br CA patients as well

as on the issue of genetic predisposition and b) independent conduct of trials of aromatase inhibitors under the BIG umbrella.

S44 Review of Italian breast cancer study group (GROCTA) trials

F. Boccardo, A. Rubagotti, D. Amoroso. *On behalf of GROCTA, National Tumour Institute, Genoa, Italy*

The 1st GROCTA trial was aimed at comparing 5-yr TAM treatment to 10 CT cycles (6 CMF followed by 4 Epi-doxo monotherapy courses) in a group of 504 pre- postmenopausal, node +ve, ER +ve breast ca. pts. This study also included an arm combining TAM with CT, 10-yr results (15-yr results will be presented at the meeting) showed no difference between TAM and TAM plus CT, while both treatments were significantly superior to CT alone. Subgroup analysis according to menopausal status, no. of involved nodes, T size and T grade yielded comparable results. The results of this study prompted us to activate 2 further studies in ER +ve women. A confirmatory study (GROCTA 02) was performed in 244 pre- perimenopausal pts by comparing 5 yrs of TAM treatment (plus 2 yrs of GOS) to 6 CMF cycles. Again no difference has emerged so far between TAM and CMF at a m.f.u. time of 53 mos while CT appeared to be more toxic. Postmenopausal women were scheduled to receive 3 yrs of TAM treatment and then to be randomly allocated to further 2 yrs of TAM or to 2 yrs of low-dose AG (GROCTA 04B). This trial explored the possibility to circumvent TAM resistance with the sequential administration of an aromatase inhibitor. 659 pts have been entered since Sept. 92, 370 of whom have been randomized to TAM (n = 187) or AG (n = 183). Groups are well balanced with respect to age and major prognostic factors. Preliminary results (m.f.u. time = 36 mos) show no major difference in pts outcome, though AG was more toxic than TAM, confirming the feasibility of this approach. Therefore a new trial (ITA trial) with a similar design but employing a less toxic and possibly more potent aromatase inhibitor, i.e. anastrozole, in place of AG will be activated in 1998. The GROCTA 03 study investigated the potential superiority of alternating adjuvant CT over standard CMF. This study, which included 107 node +ve premenopausal women and was restricted to ER −ve pts, was prematurely closed because more pts allocated to the triple alternated CT appeared to have relapsed and died at the first interim analysis. Another innovative approach, i.e. the use of HD-CT, was explored by the GROCTA 06 trial which included 53 pts with 10+ nodes and an age of ≤55 yrs. These pts were scheduled to receive 3 standard CEF cycles

followed by one cycle of HD-CT (CYC, 5 g/m^2; VP-16, 1.5 g/m^2; CDDP, 150 mg/m^2) without any form of bone marrow rescue. This HD-CT program proved to be feasible without life-threatening side effects in most pts. However, it was not superior to CMF-based CT we had previously employed in a comparable group of pts in previous GROCTA trials. These findings prompted us to explore new HD-CT programs with the use of peripheral stem cell support and in addition the possible value of new drugs such as taxol and vinorelbine. New generation trials will explore also the value of new prognostic indicators such as tumour proliferative activity, which are prospectively used to allocate pts to different treatment options.

S46 Review on current trials of the German adjuvant breast cancer group (GABG)

M. Kaufmann. *GABG, Germany*

Objectives of currently active randomized trials of the GABG in women with primary breast cancer are:

(1) Risk orientated selection of patients by menopausal status, nodal involvement and hormonal receptor content
(2) Chemo-endocrine or endocrine-endocrine sequences in pre- and postmenopausal patients
(3) Chemo or endocrine therapy in premenopausal patients
(4) Reduction of local treatment (axillary surgery, radiotherapy)
(5) Dose-intensification in high risk patients
(6) Primary chemotherapy in operable breast cancer

The trial for an individual patient can be identified by the scheme as shown in the table below.

Table S46

Preoperative: <70 J., T-size >3 cm, N0–1, M0: primary chemotherapy: Doxorubicin + Docetaxel >70 J., T-size <3 cm, N 0, M0: GABG G: breast surgery +/− axillary dissection + TAM 5 yrs. *Postoperative:* (pT1–3, R0, M0, <70J.):

Status	Hormonal receptor	Nodal status			
		N 0	N 1–3	N 4–9	N 10+
Premenop.	R+	GABG A: Zol vs CMF × 3	ZEBRA (closed): Zol vs CMF × 6		GABG E: E_{120} vs. EC-CMF;
	R−	GABG B: CMF × 3 +/− Zol		GABG B*: EC × 4-CMF × 3 +/− Zol	Zander Trial;
Postmenop.	R+	T <1 cm, G 1–2 Lo Ro GBSG V: +/− Tam +/− RT		T >1 cm; N 0–9: ARNO-Trial Tam 2 yr. – Arimidex 3 yr. vs. Tam 5 yrs	IMA Trial;
	R−	GABG D: CMF × 3 +/− Tam		GABG D*: EC × 4-CMF × 3 +/− Tam	