Breast Cancer Society. The clinical response defined as complete (CR) or partial (PR) response was assessed by caliper, mammography, or ultrasound. BCS rate and adverse events were also evaluated.

Results: Forty-four pts were enrolled and all of them were eligible. The median age was 60 years (range, 48–68). Stage IIA, IIB, IIIA and IIIB were the disease of 26, 8, 4 and 6 pts, respectively. ER and PR positive tumor was in 32 pts, and ER positive and PR negative tumor was in 12 pts. Of 44 eligible pts, three discontinued 4-months EXE due to hematological disorder (grade 3), dizziness (grade 2) or genital bleeding (grade 1), and underwent surgery. There were a few other adverse events, most of which were grade 1. In 41 pts, CR and PR were found in 0 and 27 pts, respectively; clinical response rate was 66%. Stable disease (SD) and progressive disease (PD) were found in 9 (22%) and 5 (12%), respectively. Three pts underwent chemotherapy because of PD. Eight pts refused surgery due to PR or SD after 4-months EXE, and continued EXE. The pathological response was obtained in 13 (43%) of 30 pts who underwent surgery after 4-months EXE; grade 1b in 9 and grade 2 in 4 pts. BCS was performed in 28 pts (93%).

Conclusions: Neoadjuvant EXE is effective and well tolerated in hormone-sensitive, operable breast cancer in postmenopausal pts.

369 Poster

Epirubicin plus cyclophosphamide vs. weekly paclitaxel as primary systemic therapy in patients with stage II and III breast cancer: randomized phase II study

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Background: Primary systemic therapy (PST), also known as upfront, induction or neo-adjuvant therapy, is given before the standard loco-regional therapy. Not only may it have an effect on potential micro-metastases, but it also has an effect on tumor growth. Response and survival rates achieved by anthracycline and paclitaxel (P) (q 3 weeks (W)) patients (pts) with metastatic breast cancer (BC) are comparable (ECOG1193). Weekly P is expected to produce higher response rates and lower hematological toxicity than tri-weekly P for PST (MDACC2002). The aim of this study was to evaluate the activity and toxicity of weekly P therapy compared with epirubicin (E) plus cyclophosphamide (C) therapy for stage II and III BC with PST.

Methods: Pts with histologically confirmed BC, stage II or III, performance status 0–2, and absence of prior chemotherapy were randomized to either Arm A (EC: E 75 mg/m^2 and C 600 mg/m^2 every 3 W for 4 cycles) or Arm B (weekly P: P 80 mg/m^2 weekly for 12 W). Pts received PST for 12 W, then underwent surgery. All pts received a cross-over regimen as adjuvant chemotherapy after surgery.

Results: As of Sep 2005, 149 pts have been recruited. One hundred and thirty-two pts (Arm A: n = 67, Arm B: n = 65) were evaluable. The clinicopathological characteristics of pts (age, tumor size, stage, hormone receptor (HR) and HER2 status) were well balanced in the two arms. Overall response rate (OR) was 65.7% in Arm A and 66.2% in Arm B. OR in HER2-positive pts was 66.7% in Arm A and 73.9% in Arm B, but there was no significant difference. OR in HR negative pts were equal in both arms. The incidence of grade 3/4 neutropenia (38.6% vs 2.3%, $p < 0.001$) and leukopenia (33.3% vs 0%, $p < 0.001$) were lower in Arm B than in Arm A, while that of nausea(27.5% vs 8.2%, $p < 0.02$) was higher in Arm A. Vomiting and mucositis were more frequently seen in Arm A than in Arm B, but there was no significant difference. The incidence of neuropathy (6.0% vs 52.8%, $p < 0.001$) was higher in Arm B.

Conclusions: Interim analysis of 132 pts suggested that weekly P was associated with lower toxicity than EC therapy, but more frequently induced neuropathy. OR was similar in both therapies. Therefore, induction of PST by weekly P therapy seems to be promising. We are further investigating the pathological response and accrual is still proceeding.

370 Poster

The effect of pathological response of multicenter phase II trial of fluorouracil, epirubicin, cyclophosphamide (FEC 100) followed by docetaxel (DOC 75) in primary operable breast cancer (JBCRG01: Japan Breast Cancer Research Group)

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Introduction: Preoperative systemic therapy (PST) has been widely used in the treatment of operable breast cancer. This study was designed to evaluate clinical and pathological response, safety, breast conservation (BCS) rate, survival, and translational research of FEC followed by DOC as PST in patients (pts) with operable breast cancer.

Patients and Methods: Eligible patients had primary operable breast cancer with $T_{1c-3}N_0M_0$, $T_{1-3}N_1M_0$, no prior chemotherapy, age 20–60, ECOG Performance Status 0–1, adequate hematological, renal, hepatic and cardiac function, and written informed consent. Preoperative chemotherapy consisted of 4 cycles of FEC (F: 500 mg/m^2, E: 100 mg/m^2, C: 500 mg/m^2) every 3 weeks followed by 4 cycles of DOC (75 mg/m^2) every 3weeks.

Results: From June 2002 to November 2004, 202 pts were enrolled. The median pts age was 46 (range, 25–60). All patients had ECOG Performance Status of 0. Premenopausal was 73%. Tumor stage: T1/T2/T3 7/73/20%. Node positive was 57%. Hormone status: ER positive; 67%, PgR positive; 51%, ER/PgR both positive was 49%. HER2 (IHC) status: 0/1+/2+/3+/unknown 34/27/18/19/2%. Relative dose intensity was 98% for FEC and 95% for DOC. The overall response rate was 73% [95% confidence interval (CI) 66%-79%], with 23% CR, 51% PR. Addition of DOC improved overall response rate from 60% to 73%. BCS was 83%. FEC-DOC treatment, grade 3–4 hematological toxicity included leucopenia 41%, neutropenia 52%, and febrile neutropenia 20%. Grade 3 non-hematological toxicity included nausea 8%, vomiting 6%, fatigue 2%, neuropathy 1%, and myalgia/arthralgia 1%. There were no reports of grade 4 non-hematological toxicity. For pathologic response 190 pts were evaluated by central review. pCR rate was 23% (43/190) [95% CI 17%-29%]. The higher pCR rate was obtained in ER−/PgR−/HER2(3+) pts than in ER+/PgR+/HER2(0) pts [65%(13/20) vs.13%(4/31)].

Conclusion: This is the first multicenter trial in Japan to study of FEC 100 followed by DOC 75 as primary therapy for early stage breast cancer. This regimen was effective and well tolerated therapy for Japanese patients. The results of pathological response suggest that ER/PgR both negative and HER2 positive are correlated with pathological response. From now on relationship between pathological response and prognosis will be analyzed. Further we will analyze apoptosis-related factors.

371 Poster

The relationship of positive steroid receptor (SR) status with disease outcome in patients treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil (A-CMF) chemotherapy (CHT) and adjuvant endocrine therapy

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Introduction: There is an opinion that SRs are predictive markers for the response not only to endocrine therapy, but also to chemotherapy, with SR-positive breast cancers being less sensitive to chemotherapy. The purpose of this analysis was to determine the relationship of positive SR status with disease outcome in patients treated with adjuvant chemotherapy and adjuvant endocrine therapy.

Patients and Methods: We evaluated a group of 482 early breast cancer patients, diagnosed from 1986 to 1994, who were treated either with adjuvant A-CMF CHT (N = 172), or adjuvant endocrine therapy [ovarian ablation (OA) by irradiation for premenopausal (N = 139), or tamoxifen (TAM) for postmenopausal women (N = 171)]. All patients were either node negative with grade 3 breast cancers, or had 1–3 positive nodes regardless

of tumor grade. If PgR negative, A-CMF CHT was given, while in a case of PgR positive disease, adjuvant endocrine therapy was introduced. A group of patients with SR-positive tumors defined as ER-positive/PgR-positive, ER-positive/PgR-negative, and ER-negative/PgR-positive were separated and divided according to menopausal status. Among these premenopausal (N = 196) and postmenopausal (N = 193) women disease-free survival (DFS) and overall survival (OS) were compared between women treated with A-CMF CHT and adjuvant endocrine therapy.

Results: Significantly more premenopausal patients treated with A-CMF CHT had grade 3, PgR negative breast tumors (Chi-square tests $p = 0.049$, $p < 0.001$ respectively), while significantly more women treated with OA had positive lymph nodes (Chi-square test, $p = 0.007$). In postmenopausal groups, significantly more women treated with A-CMF CHT had lower PgR (Chi-square test, $p < 0.001$), node negative status (Chi-square test, $p = 0.003$) and less frequently received postoperative radiotherapy (Chi-square test, $p < 0.001$) compared to postmenopausal patients treated with adjuvant TAM. There was no difference in DFS and OS between premenopausal women treated with A-CMF CHT and those treated with OA. However, significantly more postmenopausal patients, treated with A-CMF CHT, developed disease relapse comparing to postmenopausal women treated with adjuvant TAM (Chi-square test, $p < 0.001$), with local recurrences and bone metastases occurring significantly more frequently (Chi square tests, $p = 0.01$, $p = 0.006$, respectively). Furthermore, postmenopausal women treated with A-CMF CHT had significantly worse DFS (Log rank test, $p = 0.013$) compared to TAM group, while there was no difference in OS between the two groups.

Conclusion: Our results showed that SR might have some value as a predictive factor for the response to A-CMF CHT at least in postmenopausal women with SR-positive breast cancers.

372 Poster

Prospective phase II study of: neo-adjuvant doxorubicin followed sequentially by cisplatin/docetaxel in locally advanced breast cancer

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Background: Neoadjuvant (primary) chemotherapy as part of multimodality treatment is increasingly used as standard of care for patients (pts) with locally advanced breast cancer.

We conducted a prospective study using Doxorubicin 75 mg/m^2 q 3 weeks × 3 cycles followed sequentially by Docetaxel 75 mg/m^2 and Cisplatin 75 mg/m^2 q 3 weeks × 3 cycles. All pts had definitive surgery followed by Radiation therapy, +/− Tamoxifen. Primary end points were pathologic complete response (pCR), secondary endpoints were, safety, rate of conservative surgery and overall survival.

Material: Eligible pts included biopsy proven invasive breast cancer, T2-T4 (primary ⩾4−10 cm) N0-N2, M0. 59 of 60 enrolled pts completed treatment one patient refused surgery after the completion of 6 cycles of chemotherapy were excluded from the analysis, Premenopausal: 68%, median age: 41 yrs (24−60), median tumor size: 6.0 cm (4−10), Stage IIB: 31% and IIIA/IIIB: 68%, both ER/PR positive: 53%, Her2/neu (3+) by IHC staining: 29%, Her2/neu (+2) equivocal: 20% were all are FISH negative. All patients had negative metastatic workup.

Results: 59 pts are evaluable for analysis: clinical complete response was seen in: 44%, clinical partial response in: 56%. Breast conserving surgery was performed in: 44%, and MRM in: 56%. Pathological complete response (pCR) in the breast was: 31%, in axilla were: 37%, breast and axilla were 22%.

Grade 3−4 Toxicities: febrile Neutropenia (13%), nausea−vomiting (12%), mucositis (10%), weakness/asthenia/weight loss (12%). Overall at follow up of 50 months the DFS & OS (62% and 87%).Patients who achieved complete pathologic response both in breast and axilla the DFS and OS were (100%).

Conclusion: Sequential combination of Doxorubicin followed by Docetaxel/Cisplatin is a safe, feasible and active combination, that offer the possibility of conservative surgery and associated with high clinical and pathologic response, further investigation of this combinations are warranted.

373 Poster

Improving breast cancer survival – trends in node negative and node positive disease

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Aim: To determine any improvement in recurrence and survival in node negative and node positive breast cancer patients between 1988 and 1999.

Methods: The study was a retrospective database review of 890 breast cancer patients diagnosed between 1988 and 1999. Patients were divided into 2 groups according to the year of diagnosis (group I: 1988–1994; group II: 1995–1999). Recurrence free survival (RFS), breast cancer specific survival (BCSS) and overall survival (OS) was calculated by Kaplan-Meier life table analysis and compared using the log rank test with both groups stratified for lymph node status.

Results: There were 404 patients in group I and 486 patients in group II. 273 patients in group I and 320 patients in group II were node negative.

5-year RFS in node negative patients was 84% in group I versus 87% in group II ($p = 0.20$), BCSS was 92% in both groups ($p = 0.89$) and OS was 85% in both groups ($p = 0.95$). In node positive patients the 5-year RFS was 57% in group I and 69% in group II ($p = 0.01$), BCSS was 70% versus 78% ($p = 0.047$) and OS was 67% versus 73% ($p = 0.10$).

The use of systemic adjuvant therapy was significantly increased in group II, for node negative (chemotherapy 6% versus 18%, $p < 0.001$; endocrine therapy 74% versus 90%, $p < 0.001$) and for node positive patients (chemotherapy 33% versus 55%, $p < 0.001$; endocrine therapy 81% versus 92%, $p = 0.004$)

Conclusion: The increased use of systemic adjuvant therapy in node negative and node positive breast cancer patients between 1995 and 1999 was reflected in a significant improvement in RFS and BCSS in patients with node positive disease. Patients with node negative disease did not demonstrate any significant differences in recurrence or survival.

374 Poster

Neoadjuvant capecitabine (X), docetaxel (T) ± trastuzumab (H) for patients (pts) with locally advanced breast cancer (LABC): preliminary safety and efficacy data from a multicentre phase II study

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Background: 3-weekly XT is highly active in metastatic breast cancer, with significantly superior response rates, time to progression and overall survival vs. T alone. X and T are synergistic with H in HER2-positive tumours. We evaluated the efficacy and safety of XT±H as neoadjuvant therapy for LABC.

Materials and Methods: Pts with newly diagnosed invasive stage III inoperable LABC (cT4 and/or cN2−3) received X (900 mg/m^2 orally bid d1−14) + T (36 mg/m^2 i.v. d1&8) q3w x6, followed by surgery and radiotherapy. Pts with HER2-positive tumours (IHC 3+ or FISH+) also received H (8 mg/kg on d1 of the first 3w cycle and 6 mg/kg on d1 of subsequent cycles). Safety was evaluated after each cycle, clinical response after 3 and 6 cycles, and pathological complete response (pCR) postoperatively. pCR was defined as no residual invasive tumour in breast and axilla.

Results: To date, 30/51 pts have completed neoadjuvant chemotherapy (26 pts XT, 4 pts XT+H) and surgery. Baseline characteristics are: median age 50 years (range 25−74), median ECOG PS 0 (range 0−1), ER/PR/HER2+ status 74/61/16%. The most frequent grade 3/4 treatment-related toxicities were diarrhoea (16%), HFS (10%) and stomatitis (10%). Dose reductions were applied because of grade 2−4 adverse events (stomatitis, HFS, diarrhoea, vomiting, peripheral neuropathy and skin rash) in 11 pts and because of neutropenic fever in 2 pts. Therapy was prematurely interrupted because of disease progression (1 pt), capillary leak syndrome (1 pt), infection (1 pt), fever of unknown origin (1 pt) and psychological intolerance (1 pt). The overall response rate was 90%, including 2 CRs (7%) and 25 PRs (83%). A further 2 pts had stable disease (7%). pCR was achieved in 2 pts who completed 6 cycles of XT (8%) and in 2/4 pts (50%) after 6 cycles of XT+H. Most pts received postoperative anthracycline-based chemotherapy (4−6 cycles of