lack of interactions between anastrozole and other drugs metabolized by cytochrome P450 enzymes (1). We report on four clinical trials which showed that anastrozole did not interact with tamoxifen, antipyrine, cimetidine or warfarin.

The effect of anastrozole on tamoxifen pharmacokinetics (PK) was assessed in a randomized, double-blind, placebo-controlled trial involving 34 post-menopausal women with early breast cancer, who were already receiving tamoxifen (20 mg daily) as adjuvant therapy. These patients were randomised to also receive either anastrozole or placebo. Randomised therapy was given for 28 days from Day 0. There was no evidence of anastrozole having any significant effect on the blood levels of tamoxifen compared to placebo ($p = 0.919$). As expected, the oestradiol levels were significantly lower in the group of patients that received anastrozole than those receiving placebo ($p < 0.001$). Suppression of oestradiol levels in the combination group, was consistent with that seen in studies of patients treated with anastrozole alone.

The effect of anastrozole on warfarin PK/pharmacodynamics was assessed in 16 healthy male volunteers in a 2-way crossover trial. The results showed that anastrozole did not significantly affect the area under the curve, clearance, half-life and unbound concentrations of S- and R-warfarin. Additionally, anastrozole did not produce clinically relevant changes in the pharmacodynamic effects of warfarin.

The effect of anastrozole on antipyrine (a marker substrate of CYP activity) PK was assessed in 24 post-menopausal women (n = 12 each for anastrozole and placebo groups). No significant differences were noted in antipyrine PK parameters, compared to placebo.

The effect of cimetidine (non-specific inhibitor of various CYP enzymes) on anastrozole PK was assessed in 13 post-menopausal women. Cimetidine did not significantly affect anastrozole PK parameters.

These data show that anastrozole has no interaction with these commonly used drugs and marker substances; this is an important property for a drug potentially to be used in the long term adjuvant treatment of breast cancer.

[1] Grimm SW and Dyroff MC. *Drug Metab. Dispost.* 25, 598–602 (1997)

P101 Randomized trial of two versus four years of adjuvant tamoxifen (AT) for postmenopausal women with node positive breast cancer

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Randomized trials of AT for early stage breast cancer have shown significant reductions in the annual rates both of recurrence and of death. Most of these trials compared 1 or 2 years of AT with no adjuvant treatment. A controversy exists about the optimum duration of AT.

Patients and Methods: In 1986 we began a prospective randomized study to compare the efficacy of two different time-span of AT. Women were eligible for the study provided that they had 60–75 years old with primary breast cancer and positive axillary nodes which primary surgery was a modified radical mastectomy. Tamoxifen, 20 mg per day, was initiated within 60 days after mastectomy. No other type of adjuvant therapy was allowable. All patients without recurrence in the first two years were randomly assigned to continue or not AT for two further years.

Results: 288 women were randomized to one of the two schedules. Baseline characteristics were similar but in four years AT group there was a some larger proportion of women with 4 or more positive nodes (40% vs. 32%, $p = 0.158$). With a median follow-up of 5 years, 113 patients have recurred (62 of 142 undergoing AT for two years, and 51 of 146 undergoing AT for four years). Estimated five years – from randomization- disease free survival (DFS) was 55% for the 2 years AT group and 66% for the 4 years AT group ($p = 0.036$). When nodes group (1–3 vs. 4 or more) was accounted for in Cox's proportional hazards model, the effect of prolonged AT treatment on DFS remained significant (hazd ratio 2 vs. 4 years, 1.310, $p = 0.007$). When all causes of death were considered, the difference in overall survival among both groups of AT was not significant ($p = 0.329$). Multivariate analysis showed that 4 or more positive nodes ($p = 0.003$) and age ($p = 0.025$) were related with a significantly inferior overall survival.

Discussion: Our results suggest that, in relation to two years, four years of AT does improve the DFS in this group of women. The reduction of risk is similar to other study on this topic and the benefit is alike for both groups of nodes. We fail to detect significant differences in overall survival, competing causes of death and a still short follow-up could justify these results.

P102 Adjuvant high-dose medroxyprogesterone acetate (HD-MPA) for early breast cancer. 13 Years update of a multicenter randomized trial

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260 node negative (NN) and 281 node positive (NP) early breast cancer patients were randomized after adequate surgery to receive either no further medical treatment (group A) or an hormonotherapy with HD-MPA (500 mg IM daily for 4 weeks the 500 mg twice weekly for the next 5 months) (group B). NP patients received also 6 monthly courses of IV CMF. Patients characteristics were well balanced among both groups. Toxicity of MPA was manageable (weight increase in most patients and usual side-effects linked to progestin use in a maximum of 16% of patients in group B). In NN patients, at 13 years median follow up, relapse free survival (RFS) was significantly improved in HD-MPA arm (A: 0.54 vs B: 0.69 – p 0.004). This was observed for the whole group as well as in all prognostic sub-categories (age <50; > = 50; menopausal status; T; receptor categories; type of surgery). Differences were less striking in > = 50 years patients, as RFS curves tended to join. These differences in RFS were translated in a survival benefit in younger patients (A: 0.65; B: 0.81 – p 0.06). In the NP group, RFS and overall survival (OS) were not different at the whole group level or as regard T, number of positive nodes, receptor categories, type of surgery or radiotherapy. However a striking difference was observed when patients were split according to age (<50; > = 50) or menopausal status. If older patients benefited from the combined treatment (at 13 years RFS: A: 0.34, B: 0.59 – 0.002; OS: A: 0.48, B: 0.56), younger patients had a significantly worse prognosis when treated with CMF + HD-MPA, (at 13 years: RFS: A: 0.64, B: 0.34 – $p < 0.01$; *OS: A: 0.77, B: 0.54* – $p < 0.01$). These results were observed despite the fact that, irrespectively of age, MPA-treated patients could tolerate higher dose-intensities and dose-intensity procucts of CMF.

In conclusion, a clearcut adjuvant impact of HD-MPA was evidenced namely in <50 years NN early breast cancer, ie, in *premenopausal patients.* However, in less than 50 years NP patients, HD-MPA had a negative adjuvant impact both on RFS and OS. These results contrast with the results obtained in older NP subjects and with the significant adjuvant impact of HD-MPA observed in NN patients.

P103 What threshold for adjuvant tamoxifen in older breast cancer patients? A decision analysis

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Background: The consensus panel on the last St-Gallen conference tried to define adjuvant treatment according to risk categories. In the lowest risk category, the decision between no treatment or hormonotherapy was left optional. This study looks at the threshold risk of relapse (RR) at which tamoxifen offers benefit, and the threshold at which a 1% benefit in 5 or 10 years relapse rate or survival is obtained in older women. We studied also the way these threshold were influenced by the level of comorbidity.

Methods: A Markov model analysis was conducted. Data from the litterature retrieved by Medline and cross references were used. We hypothesized 5 years of tamoxifen use in receptor positive tumors.

Results: In women up to the age of 85, the threshold for an absolute positive effect on survival was minimal. The threshold RR allowing for a 1% reduction in mortality at 10 years was a 12% 10 years RR for a healthy 65 years old patient, and 21% for a patient in poor health. At 85 years, a 1% benefit in 10 year mortality cannot be obtained. However, for a 1% reduction in mortality at 5 years, the threshold 10 year RR is 31% for a healthy patient and 39% for a sick patient. Reduction in relapse is much less sensitive to age and comorbidity. For a 1% gain in relapse at 5 years, the threshold RR is 7% in a healthy 85 years old patient and 8% in a sick patient.

Conclusions: The threshold for a 1% improvement in 10 years relapse-free survival or overall survival is near the limit between minimal and low risk tumors in the St Gallen recommendations for healthy elderly with hormone-receptor positive breast cancer. For patient in their eighties, quality of life issues become a major consideration, since tamoxifen will decrease the rate of relapse without a major impact on survival in low-risk tumors.

P104 Adjuvant chemotherapy plus alternated hormonal therapy (AVCF-TM) for HR+ N+ breast cancer: 13-Year results of a randomized phase III trial

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Adjuvant AVCF (Doxorubicin 30 mg/m^2 IV d1, Vincristine 1 mg/m^2 IV d2, Cy-

clophosphamide 300 mg/m^2 IV d3–6, Fluorouracil 400 mg/m^2 IV d3–6, every 28 days) improves survival of N+ breast cancer (BC) patients (pts). In 1981, Tamoxifen (TAM) had recently been shown to increase the expression of the Progesterone Receptor in breast cancer cell lines. This notion, together with the idea that chemo-hormonotherapy might surpass chemotherapy alone in Hormonal Receptor-positive (HR+) BC pts, was the basis of the present randomized phase III trial, conducted between 1981 and 1985 in 6 french cancer centers.

Patients and Methods: 238 pts bearing HR+ Node-positive (N+) BC were randomized to either monthly AVCF for 6 courses (n = 134), or the same plus an alternance of oral Tamoxifen, 30 mg daily for 14 days, and oral Medroxyprogesterone Acetate, 500 mg daily for 14 days (AVCF-TM), during one year (n = 104). Median age was 53 years. 54% of the pts were postmenopausal. 46% also received locoregional radiation therapy. Most tumors were T1 or T2 (84%). SBR histoprognostic grades, determined in 70% of the pts, were as follows: grade 1, 26%; grade 2, 62%, Grade 3, 12%. Two thirds of the pts had ^{2} 3 nodes involved. Major prognostic factors were well-balanced between both arms.

Results: 236 pts are available for final analysis. Although grade 3 to 4 acute toxicities were rare, one toxic death occurred, due to febrile neutropenia. At a median follow-up of 12.9 years (1–15), no difference could be detected between the two treatment arms in terms of Disease-Free Survival (50 vs 51%, p = 0.91) nor Overall Survival (OS) (53 vs 54%, p = 0.86). We also failed to elicit a benefit for pts over 60 years, as it had been previously described. A significant advantage in OS was noticed for the AVCF-TM arm in the SBR grade 3 subgroup of pts (p = 0.006), but the samples, although well balanced, were very small (8 and 10 pts). The incidence of contralateral breast cancer (CBC) was not different between both groups (10-year cumulative incidence 5.5 and 6.5%). However, interestingly, the median Time-To-CBC was much longer in the AVCF-TM arm: 112 (45.6–149) versus 61 (12–104) months.

In conclusion, this is the first report of the use of an alternated hormonal therapy in the adjuvant treatment of breast cancer. However, this short-duration hormonal therapy failed to add any benefit to an adjuvant anthracyclin-based chemotherapy regimen (AVCF) in HR+ N+ pts.

P105 Inhibition of Tamoxifen's therapeutic benefit by Tangeretin in mammary cancer

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Overall survival for patients with primary breast cancer is increased by adjuvant therapy with Tamoxifen. Resistance to Tamoxifen is one of the reasons for treatment failure in mammary cancer patients. Flavonoids from the diet have been implicated in this problem through direct estrogenic effects on the tumor cells or induction of Tamoxifen's liver metabolisation. Tangeretin, a citrus flavonoid with extensively studied effects on human mammary cancer cells *in vitro*, was tested in combination with Tamoxifen in tumor-bearing laboratory mice. Our model consisted of estrogen-primed female nude mice inoculated subcutaneously with human MCF-7/6 mammary carcinoma cells. Oral treatment of the mice with Tamoxifen inhibited the growth of the MCF-7/6 tumors as compared to solvent controls ($p < 0.001$ in Student's *t*-test). Tangeretin, added to the drinking water with Tamoxifen, completely neutralized the effect of Tamoxifen. Furthermore, Tamoxifen/Tangeretin treatment reduced the median survival time of the tumor-bearing mice as compared to the Tamoxifen-treated group (14 versus 56 weeks; p = 0.002 in Mantel-Cox Logrank test). Remarkably, the growth-inhibiting effect of Tamoxifen could be reversed upon addition of Tangeretin to the drinking water: tumor growth resumed after a median lag period of 14 weeks.

Induction of liver metabolisation of Tamoxifen by Tangeretin was ruled out. Tamoxifen concentration was not lower in tumor and tissues from Tamoxifen/Tangeretin treated mice than from Tamoxifen treated ones.

Taken together, our results plead against excessive consumption of Tangeretin-containing citrus products during the Tamoxifen treatment of mammary cancer.

P106 A lack of evidence for the genotoxicity of tamoxifen and toremifene in the human endometrium

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The association of the drug tamoxifen with human endometrial cancer has been the cause of considerable controversy. Debate has centred upon whether tamoxifen is genotoxic to human tissues, as is the case in the rat where it is metabolised to a reactive intermediate which gives rise to high levels of DNA adducts in the liver (a genotoxic event). A study exploring DNA adduct formation in human endometria, utilising Thin Layer Chromatography-^{32}P-postlabelling, found no evidence for such adducts in women treated with the drug [Carmichael *et al.* 1996 *Cancer Res.* 56 1475–9]. However, a subsequent study utilising High Performance Liquid Chromatography (HPLC)-^{32}P-postlabelling suggested that very low levels of adducts could be detected in 5 out of 7 endometrial samples from 6 patients treated with 20 or 40 mg/day tamoxifen [Hemminki *et al.* 1996 *Cancer Res.* 56 4374–7]. Through a joint-centre approach, we have sought to confirm or dispute these findings by reproducing the HPLC methodology at both Imperial College and the Institute of Cancer Research, analysing endometrial DNA from 20 patients treated with 20 mg/day tamoxifen for a period of between 22 and 65 months. We have found no evidence for the presence of tamoxifen-derived DNA adducts in any of these tissues as compared to rat adduct standards, and furthermore found no evidence for DNA adducts induced by the tamoxifen analogue, toremifene in endometria from 8 patients treated with 60 mg/day for 6 or 12 months. On the basis of this evidence and previous studies, we suggest that neither tamoxifen nor toremifene are metabolised in women to electrophiles that bind DNA in sufficient quantity to be genotoxic or carcinogenic. However, we cannot rule out the possibility that tamoxifen may modulate levels of endogenous DNA adducts or have other effects on human endometrial tissue.

P107 The 'ZEBRA' study: 'Zoladex' (goserelin) vs CMF as adjuvant therapy in the management of node positive stage II breast cancer in pre/peri-menopausal women aged 50 years or less

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'Zoladex' (goserelin) suppresses ovarian function and is an established and effective endocrine therapy for the management of advanced breast cancer in pre/perimenopausal women, convenient to administer and well tolerated. The exact role of goserelin as an adjuvant treatment for early breast cancer in pre/peri-menopausal women remains to be defined. The ZEBRA ('Zoladex' Early Breast Cancer Research Association) study was set up to evaluate goserelin in a comparative study against cytotoxic chemotherapy, the current systemic adjuvant treatment most often used in this age group.

The ZEBRA study was started in 1990 as a collaboration between Zeneca (formerly ICI) Pharmaceuticals, the German Breast Cancer Group and the University of Freiberg. ZEBRA is an open randomised clinical trial comparing goserelin (2 years therapy of one 3.6 mg depot injection every 28 days) with the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) (6 × 1 monthly cycles) in the management of node positive stage II breast cancer in pre/peri-menopausal women aged ≤50 years. Recruitment to the study was completed in December 1996 with 1640 patients enrolled. The first analysis is planned for mid-1999.

The objective of the study is to compare disease-free survival (DFS), overall survival, safety and adverse events for the two treatment arms.

Concurrently with the main study there are two additional comparisons between goserelin and CMF. These are: 1) *Bone*, where loss of bone mineral density during and after treatment is being determined in 187 patients. 2) *Quality of Life* in 1466 patients. Also, two further projects are planned: to assess the endocrine status of patients completing two years therapy with goserelin and to determine oestrogen receptor status for subgroup analyses comparing goserelin and CMF in terms of survival and DFS.

'Zoladex' is a trademark property of Zeneca Limited.

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Friday, February 27, 1998 **9.00–18.00**

Quality of Life, Toxicity

P108 Assessement of changes in life quality of breast cancer patients under adjuvant CMF-chemotherapy by means of the EORTC QLQ-C30

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The Analysis of Life Quality (LQ) is an important parameter in the evaluation of chemotherapy (CHT) nowadays. The European Organization for Research and