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

M. Gallén, C. Alonso, B. Ojeda, P. Viladiu, M. Beltrán, J. Borras, A. Pelegrí, I. Tusquets, A. Barnadas, A. Arcusa, R. Bastús, A. Balil, E. Batiste-Alentorn, M. Boleda, M.A. Badia, I. Garau, I. Guash. *A cooperative oncologic group; Passeig Marítim, 25–29, Oncologia, Hospital del Mar, Barcelona, Spain*

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

C. Focan, M. Beauduin, E. Salamon, J. de Greve, G. de Wasch, J.P. Lobelle, F. Majois, A. Tagnon, J. Tytgat, S. Van Belle, R. Vandervellen, A. Vindevoghel. *For the Adjuvant Breast Cancer Project; Les Cliniques Saint Joseph, Liege, Belgium*

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

M. Extermann, L. Balducci, G. Lyman. *H. Lee Moffitt Cancer Center at the University of South Florida, Tampa, FL, USA*

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

M. Di Palma, S. Delaloge, S. Guérin, P. Fargeot, T. Conroy, P. Chollet, J.L. Misset. *For the Groupe OncoFrance; S.M.S.T, Hôpital P. Brousse, Villejuif, France*

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