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The HOT study: Hormone replacement therapy opposed by low dose of tamoxifen. A phase III trial of breast cancer prevention with low dose tamoxifen in HRT users: Background and rationale of the project

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While life expectancy has grown by approximately 30 years in the last century in western countries, age at menopause has increased by 2-3 years only. Thus women are exposed to postmenopausal symptoms and disorders for a considerable period of their lifetime,and the management of these frequent disorders is an important public health essue. Although the concept of a benefit of HRT on life expectancy mostly derives from epidemiological studies, there is good evidence that the use of HRT increases quality of life and has the potential to reduce overall mortality. Risks of HRT include 2-3-fold excess of VTE and a slight higher mortality from ovarian cancer in women on HRT for 10 years or longer. However the major obstacle to its widespread use is the increased risk of breast cancer. Tamoxifen can be classified as a first generation selective estrogen receptor modulator. It is widely used for palliative endocrine treatment of advanced breast cancer and as adjuvant therapy to control mocrometastatic relapse and new primaries in women surgically treated for early breast cancer. In 1992 in the NSABP-P1 trial tamoxifen was used in comparison to placebo for prevention of breast cancer in at-risk women. Following the results of this study, tamoxifen has been registered in the USA for the reduction of risk in women at increased risk as, assessed by the Gail model. Recent studies suggest that the standard dose of tamoxifen may be reduced to one quarted without significant loss of its beneficial biological effects. The aim of the present study is to assess whether tamoxifen administratrion at a low dose (5 mg) for 5 years reduces the risk of breast cancer in women undergoing hormone replacement therapy or willing to start it. The primary endpoint is the incidence of ductal in situ carcinoma and invasive breast cancer. After the 5 years of trewatment a follow up period of 5 years is foreseen. The secondary endpoints include incidence of: other non invasive breast disorders, endometrial cancer, all other cancer, bone fracture, cardiovascular events, venous thromboembolic events, overall mortality.

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A randomized 2 x 2 biomarker trial of low-dose tamoxifen and fenretinide in premenopausal women at-high risk for breast cancer

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Tamoxifen and fenretinide have been shown to reduce breast cancer incidence in pre-menopausal women at increased risk in clinical trials. Their combination is synergistic in reducing mammary tumor formation in animal models. We conducted a double blind clinical trial in two Italian institutions to assess the interaction between the two agents on putative breast cancer surrogate endpoint biomarkers. Between October 1998 and April 2002, a total of 880 women were registered and 235 were randomized in a double dummy fashion either to tamoxifen 5 mg/d, or fenretinide 100 mg bid, or both agents, or placebo for 2 years. Women are to be followed-up for an additional three years. Premenopausal women (last menstrual period within 6 months and FSH <30 IU) were eligible if they had previously excised DCIS (57%), LCIS (13%), microinvasive breast cancer (7%), or a 5-year Gail risk >1.3% (23%). The mean ± SD age of the study population is 46.2±4.7 (range 30-57) and the mean ± SD BMI is 23.5±3.5 kg/m2. The primary outcome measures were two-fold: the change in blood insulin-like growth factor-I (IGF-I) and in mammographic percent density (Toronto method) after 2 years of intervention. Additional endpoints include changes in endometrial thickness and proliferation, presence of ovarian cysts, atypia in random fine needle aspirates and a variety of blood biomarkers. Recruitment was prematurely stopped by the DSMB based on the lack of an interaction between agents on the primary surrogate endpoint biomarkers which would not be affected by increasing the sample size to the anticipated goal set of 300 subjects. As of October 31, 2003, the mean ± SD follow-up time is 39.2±13 months and 42 subjects are still on treatment. A total of 35 subjects (14.9%) have dropped out for a variety of reasons, including 19 due to adverse events, Serious adverse events include one stage I endometrial cancer and, in the tamoxifen arm, one ischemic neuropathy of the optic nerve. So far a total of 26 primary or recurrent breast cancers have been observed. Treatment compliance as assessed by pill count and self-reporting show a greater than 80% adherence in >90% of the subjects. Biomarker measurements are ongoing and preliminary results in terms of efficacy and safety will be presented at the conference.