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### ► To cite this version:

Asgerdur Sverrisdottir, Hemming Johansson, Ulla Johansson, Jonas Bergh, Samuel Rotstein, et al.. Interaction between goserelin and tamoxifen in a prospective randomised clinical trial of adjuvant endocrine therapy in premenopausal breast cancer. *Breast Cancer Research and Treatment*, 2011, 128 (3), pp.755-763. 10.1007/s10549-011-1593-0 . hal-00646007

**HAL Id: hal-00646007**

**<https://hal.science/hal-00646007>**

Submitted on 29 Nov 2011

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# **Interaction between goserelin and tamoxifen in a prospective, randomised clinical trial of adjuvant endocrine therapy in premenopausal breast cancer**

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**Abstract:** Ovarian ablation improves survival in premenopausal early breast cancer, but the potential added value by luteinizing hormone-releasing hormone (LHRH) agonists to tamoxifen, is still not clear. The purpose of our study is to examine the efficacy of the LHRH agonist goserelin for adjuvant therapy of premenopausal breast cancer, the role of interaction between goserelin and tamoxifen, and the impact of estrogen receptor (ER) content. A total of 927 patients were included in the Stockholm part of the Zoladex in Premenopausal Patients (ZIPP) trial. They were randomly allocated in a 2 x 2 factorial study design to goserelin, tamoxifen, the combination of goserelin and tamoxifen or no endocrine therapy for 2 years, with or without chemotherapy. This is formally not a preplanned subset analysis presenting the endpoint first event. In this Stockholm sub-study, at a median follow up of 12.3 years, goserelin reduced the risk of first event by 32 % (P = 0.005) in the absence of tamoxifen, and tamoxifen reduced the risk by 27 % (P = 0.018) in the absence of goserelin. The combined goserelin and tamoxifen treatment reduced the risk by 24 % (P = 0.021) compared to no endocrine treatment. In highly ER positive tumours, there were 29% fewer events among goserelin treated (P = 0.044) and a trend towards greater risk reduction depending on the level of ER content. The greatest risk reduction from goserelin treatment was observed among those not receiving tamoxifen (HR: 0.52, P = 0.007). In conclusion, goserelin as well as tamoxifen, reduces the risk of recurrence in endocrine responsive premenopausal breast cancer. Women with strongly ER positive tumours may benefit more from goserelin treatment. The combination of goserelin and tamoxifen is not superior to either modality alone. With the limitations of a subset trial, these data have to be interpreted cautiously.

**Keywords:** breast cancer; premenopausal; goserelin; tamoxifen; interaction; randomised

## Introduction

The potential added value by luteinizing hormone-releasing hormone (LHRH) agonists to tamoxifen in the adjuvant setting for premenopausal breast cancer, remains unclear. In addition, the optimal timing and duration of LHRH agonist treatment is yet to be defined [1-4]. Nevertheless, it is clear that ovarian ablation improves survival in premenopausal women with early breast cancer [3]. Results from trials using LHRH agonists in the adjuvant setting have indicated significant benefit in terms of prolonged disease-free survival and improved survival with 2 years of treatment, regardless of other systemic treatment. Treatment induced ovarian ablation, whether by endocrine- or chemotherapy, radiation or surgery, results in increased disease-free survival and overall survival in premenopausal endocrine responsive breast cancer [4]. Remaining research questions include the benefit of LHRH agonists, in addition to tamoxifen, and if LHRH agonists have a role among those not achieving amenorrhea during cytotoxic chemotherapy. Moreover, efficacy of endocrine treatment in relation to estrogen receptor (ER) status is mainly established among postmenopausal women, and the different endocrine milieu in premenopausal women may affect the predictive ability of ER status [5-8].

Overview data on the use of LHRH agonists have not shown therapeutic benefit with combination endocrine therapy versus tamoxifen or goserelin alone in women treated with chemotherapy [3]. The ZIPP trial was included in the overview and it is the largest one assessing the integration of LHRH agonists, into hormonal therapy.

Results from the ZIPP trial have been reported and are recently updated [9, 10]. At a median follow-up of 12 years, two years treatment with goserelin was as effective as two years of tamoxifen. In those not treated with tamoxifen, there was a large survival and recurrence benefit with goserelin (13.9% fewer events, 95% confidence interval (CI), -19.4 to -7.5), and the addition of tamoxifen to goserelin showed marginal but not statistically significant

improvement (2.8% fewer events, CI -7.7 to 2.0) [10]. One of the limitations of the ZIPP trial is that randomisation was not strict factorial at all participating study sites. Some centres gave tamoxifen electively and only randomised to goserelin or no goserelin. A recent Cochrane review pointed out that results from the trial have not been reported separately for patients who underwent randomisation to both an LHRH agonist and tamoxifen [11].

As the research question of the benefit of tamoxifen in addition to an LHRH agonist remains unsettled, it was considered reasonable to analyse the Stockholm part of the ZIPP trial separately, and examine if the indirect comparisons of the overall trial can be reproduced in the Stockholm cohort. The Stockholm study was initially planned as a separate trial, but as it was found to be underpowered as a stand-alone trial for survival analysis, collaboration with centres in Sweden, UK and Italy (ZIPP trial) was established. This late and formally not planned separate analysis of the Stockholm cohort, presents therefore only the endpoint event free survival (EFS). The Stockholm part of the trial is a strict randomised 2 x 2 factorial subset of the ZIPP trial. In other centres, the analysis made in comparison to the control group, is indirect concerning the tamoxifen treatment, since the drug was prescribed electively. In addition, the Stockholm cohort is the only one with complete information on nodal status and whether chemotherapy was given or not. Furthermore, ER status of the primary tumour was available in a high proportion of all randomised women and all assays performed at a single laboratory.

## Patients and methods

The ZIPP trial was a collaboration between four research groups (Stockholm, South East Sweden, Cancer Research UK and UCL Cancer Trials Centre (CRC), United Kingdom and Gruppo Interdisciplinare Valutazione Interventi in Oncologia (GIVIO), Italy). The study was designed to determine whether the addition of goserelin and/or tamoxifen to adjuvant therapy provided benefit for premenopausal women with early breast cancer as has been described elsewhere [9].

In Stockholm all patients were included in a 2 x 2 factorial randomisation to goserelin (3.6 mg subcutaneously every 28 days), tamoxifen (40 mg daily), combination of goserelin and tamoxifen or no endocrine therapy for 2 years. Node-positive women were allocated to adjuvant CMF chemotherapy (six cycles of cyclofosfamide 600 mg/m<sup>2</sup>, methotrexate 40 mg/m<sup>2</sup> and fluorouracil 600 mg/m<sup>2</sup> intravenously days 1 and 8, every 28 days), in addition to endocrine therapy. Patients with four or more positive lymph nodes received additional loco-regional radiotherapy including the chest wall, axillary- and supraclavicular lymph nodes, 46 Gy through 4.5 weeks. Endocrine treatment was given concurrently with chemotherapy.

The randomisation was stratified in three groups based on nodal status and use of other adjuvant therapies: node negative patients who received no adjuvant chemotherapy, patients with 1-3 positive lymph nodes who received chemotherapy, and patients with four or more positive lymph nodes who received both chemotherapy and loco-regional radiotherapy (Figure 1). Randomisation was carried out by telephone to a central office where the patient identifiers were recorded before the allocated treatment was revealed to the responsible physician. Treatment allocation was based on balanced lists using the permuted block technique.

The inclusion criteria were: invasive breast cancer  $\geq 10$  mm, premenopausal menstrual status (defined as last menstruation  $< 6$  months earlier), primary surgery consisting of a mastectomy or a wedge resection plus axillary node dissection, and no clinical evidence of distant metastases. The exclusion criteria were: inoperable breast cancer, previous radiotherapy or neo-adjuvant chemotherapy, and previous or concurrent endocrine therapy.

All hormone receptor analyses on tumour samples were performed at a single laboratory, which participated in repeated control studies for receptor determination, using the same technique. The ER content was determined by isoelectric focusing on polyacrylamide gel which has been described elsewhere [12]. The receptor values were normalised to DNA content as measured by Burton and expressed as the binding capacity of estradiol in femtomoles (fmol) per microgram ( $\mu\text{g}$ ) of DNA [13]. Tumours with a receptor content equal or more than  $0.05$  fmol/ $\mu\text{g}$  DNA, were classified as ER positive, whereas tumours with estrogen content less than  $0.05$  fmol/ $\mu\text{g}$  DNA, were classified as ER negative [6]. The ER positive tumors were further sub divided into intermediate ER:  $0.05 - 0.59$  fmol/ $\mu\text{g}$  DNA and high ER:  $\geq 0.60$  fmol/ $\mu\text{g}$  DNA.

The study was designed and conducted according to ICH-Good Clinical Practice guidelines and was approved by the Karolinska Institute Regional Ethics Committee.

## Statistical methods

Time to event was calculated as time from date of randomisation to date of disease recurrence, contralateral breast cancer, other cancer or death without a reported recurrence, whichever came first. Time for alive and event-free patients, was calculated from the date of randomisation to the common end-date for follow-up, December 31 2005. Kaplan-Meier technique was used to estimate failure probability, and the log rank test was used to test for difference in time to event between treatment groups. Hazard rate ratios and 95% confidence intervals were estimated using proportional hazards regression. When assessing the main treatment effect of tamoxifen or goserelin, the other treatment was used as control. Test for interactions was performed by inclusion of product terms in the regression models. The analyses were on the basis of intention to treat. No analyses were done on the basis of treatment received. We also analysed the effect of treatment on time to first recurrence according to level of ER content, i.e. ER negative ( $< 0.05$  fmol/ $\mu$ g DNA), intermediate ER (0.05-0.59 fmol/ $\mu$ g DNA), and high ER ( $\geq 0.60$  fmol/ $\mu$ g DNA). The cut-off for the two ER positive groups was made at a level, which created equally sized groups. Data on ER content was available on 793 patients (86%). Interaction between treatments and ER content were further investigated graphically by use of Subpopulation Treatment Effect Pattern Plots (STEPP) [14]. The STEPP analysis was performed using the program `stepp_tail`, implemented in the statistical software Stata [15].

## Results

A total of 927 women in Stockholm were recruited to the study from 31 May 1990 to 8 January 1997. Of the 927 recruited women, 234 were randomised to the control (C) arm, 231 were randomised to receive goserelin (G), 231 to tamoxifen (T) and 231 to goserelin plus tamoxifen (GT) therapy. Patient characteristics were well balanced between the treatment groups as seen in table 1. Nodal status was known for all women and hormone receptor status reported for 86% of the women included in the analysis. One woman was incorrectly randomised twice and one woman was diagnosed with recurrent disease at the date of randomisation. The remaining 925 women were included in the analysis.

The common end of follow-up was January 1, 2006. After a median follow up time of 12.3 years, 166 women presented with loco-regional recurrence as a first event, 159 had a distant metastases, 54 had contra-lateral breast cancer, 50 women were diagnosed with other cancers and there were 6 deaths as first event. The overall number of deaths from breast cancer was 225 and there were 26 non-breast cancer deaths. The total number of first events was 435. There were 128 (55%) first events in the C group, 98 (42%) in G treated, 101 (44%) among T treated and 108 (47%) in the GT group.

Three main sets of analyses were carried out, first the overall effect of endocrine therapy versus no endocrine therapy, secondly the effect of goserelin with or without tamoxifen and finally the effect of tamoxifen with or without goserelin.

In the first set of analysis, the control group was used as a reference. In comparison to the controls, endocrine treatment with either goserelin alone, combined with tamoxifen or tamoxifen alone, reduced the risk of first recurrence by 32 % (CI, 0.52 to 0.89), 24 % (CI, 0.59 to 0.98) and 27 % (CI, 0.56 to 0.94) respectively (P = 0.021) (Figure 2). The second analysis showed that goserelin treatment reduced the risk of first recurrence by 16% (CI, 0.68



to 1.02). There was no additional beneficial effect of goserelin with tamoxifen, but in the absence of tamoxifen, first recurrence was reduced by 32% (CI, 0.53 to 0.89). In the third set of analysis, we examined the effect of tamoxifen. The main effect of tamoxifen was not statistically significant (HR: 0.89, CI, 0.74 to 1.08), but when examined separately for those not treated with goserelin, there was a 27% benefit for tamoxifen (CI, 0.56 to 0.95). A test for interaction between goserelin and tamoxifen was statistically significant ( $P = 0.025$ ) (Table 2, Figure 3).

When we examined the treatment effect for different levels of ER content, there was an overall effect of goserelin in the high ER group (HR: 0.71, CI, 0.50 to 0.99,  $P = 0.044$ ) and a trend towards greater risk reduction with increasing levels of ER content (Figure 4). The greatest risk reduction from goserelin treatment in the group with high ER was observed among those not receiving tamoxifen (HR: 0.52, CI, 0.32 to 0.84,  $P = 0.007$ ).

The main effect of tamoxifen in the high ER group was not significant (HR: 0.85, CI, 0.61 to 1.18) (Figure 4). Neither was there a significant risk reduction for tamoxifen alone (HR: 0.68, CI, 0.44 to 1.05,  $P = 0.081$ ). For the intermediate ER group, there was neither a main effect of goserelin (HR: 0.80, CI, 0.57 to 1.14), nor tamoxifen (HR: 0.97, CI, 0.68 to 1.38). Finally, among those classified as ER negative, there was no main effect of goserelin (HR: 1.25, CI, 0.85 to 1.82), tamoxifen (HR: 0.85, CI, 0.59 to 1.24) or combined goserelin and tamoxifen (HR: 1.03, CI, 0.63 to 1.67). In the intermediate and ER negative groups, the treatment effect of goserelin and tamoxifen, was not modified by each other (Figure 4).

## Discussion

In previously published and recently updated ZIPP trial analysis, some inconsistencies in the study design were noted, i.e. randomisation to tamoxifen had been optional in some centres [9, 10]. Subsequently, some women received tamoxifen electively. The Stockholm and GIVIO centres alone, maintained the 2 x 2 factorial randomisation throughout the trial. In addition, the Stockholm cohort was well defined according to hormone receptor content, nodal status and whether chemotherapy and/or radiotherapy was given or not.

The ZIPP trial was included in the meta-analysis of the Early Breast Cancer Overview group, which concluded that LHRH agonists alone are effective in the adjuvant setting in hormone receptor positive breast cancer, both in terms of recurrence-free and overall survival. The optimal timing and duration of use however, remains unclear and there is lack of data from randomised trials where LHRH agonists are tested against chemotherapy, with or without tamoxifen in both arms [3]. Our results from the present Stockholm sub-cohort, are in concordance with the previously published results of the conjoint ZIPP trial data, where goserelin effect on recurrence is considerable and the most marked effect is seen among those not receiving concomitant tamoxifen. The pooled trial results also showed a survival benefit not possible for us to examine here because of a small sample size. Despite the limited sample size, the strength of this report is the strict randomised design and execution of the study, as recently recommended by the Cochrane review group. This design allows a formal test of interaction which is not possible for the overall trial data of 2706 patients. Furthermore, the single laboratory analyses of ER content with a quantitative cytosol method, allowed an analysis of the effect of different receptor levels on outcome. This formal test of interaction between goserelin and tamoxifen in a randomised cohort confirms the indication made in the Hackshaw report, that tamoxifen provides no additional benefit among women treated with goserelin [10]. The same is true for the opposite, where goserelin provides no additional

benefit for tamoxifen treated. Tamoxifen is effective in extending the time to first recurrence, but only among those not receiving goserelin. The lack of additional benefit of combined endocrine therapy has previously been demonstrated in the postmenopausal adjuvant as well as the metastatic setting [16, 17]. As our study is not powered for survival analysis, the ongoing Suppression of Ovarian Function Trial (SOFT), should answer the question of the effect of combination endocrine therapy in the premenopausal setting, more decisively. In our strictly randomised cohort, the analysis of estrogen receptor levels confirms the lack of effect on ER negative women, in line with previous reports [18]. An intriguing finding is however, that the effect of goserelin increases with higher ER levels, whereas the same does not apply for tamoxifen. This may be a finding of chance, but the data indicates a clear difference, which may be based on biological grounds. Goserelin, which has stronger estrogen suppressor effect compared to tamoxifen, is potentially more effective when ER content is high. In this group, tamoxifen may not have sufficient effect to counteract the highly estrogenic milieu of premenopausal women. The STEPP plots demonstrating this effect, are however based on small subsets of patients, and the data will therefore have to be interpreted conservatively. Among postmenopausal women, earlier studies have shown a significant trend in reduction of recurrence rate with higher ER levels among tamoxifen treated, supporting the significance of stronger ER content in endocrine treatment [5-8].

Quality of life aspects and the long-term side effects are important factors to be taken into consideration when assessing improvements in adjuvant therapy. The overview has shown that goserelin is an option for women where chemotherapy is contraindicated or strongly opposed to cytotoxic drugs [3]. Premature menopause is highly probable after chemotherapy and desire for pregnancy is not uncommon after completed treatment. Moreover, some women may be reluctant to the adverse effects of permanent ovarian failure, such as infertility and accelerated bone loss. These factors have been studied extensively in the Stockholm

cohort and reported in several publications [19-22]. Our study on ovarian function showed that amenorrhea among goserelin and chemotherapy treated, was more often reversible compared to those not receiving goserelin [19]. We did not observe this effect among women who received tamoxifen in addition to goserelin. However, there was lack of power for analysis of survival effect from different endocrine treatment in the subset of women that developed chemotherapy induced amenorrhea. Results from studies examining the possible protective effect of goserelin on ovarian function are nevertheless conflicting and results from ongoing trials are awaited. Our study on bone mineral density (BMD) showed a substantial but reversible decrease in BMD after 2 years of goserelin therapy whereas the addition of tamoxifen to goserelin resulted in less changes in BMD [20]. The possible role of aromatase inhibitor (AI) treatment in combination with an LHRH agonist is not clear but the addition of AI's is likely to exaggerate the bone effects further. At present, there is limited data on this approach in the adjuvant setting, but AI's have shown a marked effect on bone metabolism. The Austrian Breast and Colorectal Cancer Study Group (ABCSCG)-12 trial showed that zoledronic acid not only counteracts effectively the demineralising effects from goserelin, but improves disease-free survival as well [2]. Accordingly, bone loss is manageable and should not restrict the use of goserelin. Further studies on the Stockholm cohort showed that sexual dysfunction as well as physical effects from goserelin diminished with time, whereas chemotherapy related symptoms were on-going at follow-up at 3 years [21, 22]

A limitation of the Stockholm study may be the 2 years of 40 mg/day tamoxifen, which was standard at the time, instead of 5 years of 20 mg/day treatment as currently recommended. In contrast to tamoxifen, 2 years of goserelin is still within the recommended treatment period, although the optimal duration of treatment is not yet determined. Another limitation is the concurrent use of chemotherapy in the trial, which may not be optimal based on the risk of endocrine therapy interaction with chemotherapy, and sequential treatment currently being

recommended as a standard. However, this concern is primarily based on the report by Albain et al, and the study lacked power to reveal significant statistical difference, although the hazard ratio indicates that concurrent therapy should not be given [23].

In conclusion, goserelin is effective in reducing risk of recurrence and improving survival in endocrine responsive premenopausal breast cancer. These effects are not enhanced further by the addition of tamoxifen, and there is a significant interaction between goserelin and tamoxifen. Quality of life is affected and side effects are considerable from goserelin, but they are manageable and moreover, reversible. This study indicates that there may be an additional subgroup of women besides the very young, i.e. those with strongly ER positive tumors, who benefit more from goserelin treatment, whereas the effect of tamoxifen does not seem to be modified by ER content. A significant interaction indicates that the effect of goserelin depends on whether tamoxifen is given or not and the effect of tamoxifen depends on whether goserelin is given or not. Our data supports, that there is no additional benefit from combination endocrine therapy in the premenopausal setting. Within the limitations of the exploratory approach and limited power as a stand-alone trial and, our results should be viewed mainly as hypothesis generating, awaiting data from ongoing trials such as SOFT.

## **Acknowledgements**

This trial was supported by the Swedish Cancer Society and King Gustav V Jubilee Fund.

Jonas Bergh's research group was supported as well by The Swedish Research Fund,

Stockholm County Council Research Funds (ALF/FoU), The Stockholm Cancer Society, The

Swedish Breast Cancer Association (BRO), Karolinska Institutet, Stockholm County Council

Research Strategy Initiative and Märit and Hans Rausing's Initiative Against Breast Cancer.

We would like to thank the following contributing physicians participating in the trial in

Stockholm: J. Einhorn, L. Perbeck, B. Cedermark, U. Ringborg, N. Wilking, L. Skoog, M.

Iiristo, G. Svane, I. Fredriksson, P. Nikolaidis, J. Frisell, K. Sandelin, P. Gunnarsson, E.

Göransson, (Karolinska University Hospital), U. Glas, A. Somell, F. Celebioglu, L

(Södersjukhuset Hospital). R. Fernstad, L. Löfgren (St. Görans Hospital), M-L. Hjalmar, K.

Dahlberg (Danderyd Hospital), E. Af Trampe, (Sophiahemmet). L. Lenner (Visby Hospital),

C. Wadström, M. Al Haider (Södertälje Hospital), T. Teve (Sabbatsberg Hospital), J.

Askegren (Huddinge University Hospital), as well as all former and present members of the

Stockholm Breast Cancer Group. Finally we like to thank the nursing staff at the breast units

at Karolinska-, Danderyd-, Huddinge- and Söder Hospitals, contributing to the logistics of the

trial, coordinating patient visits and examinations.

## Legend

**Table 1.** Baseline patient characteristics by allocated treatment

<sup>1</sup> $\geq 0.05$  fmol/ g DNA. <sup>2</sup> $< 0.05$  fmol/ g DNA.

## Legend

**Table 2.** Effects of goserelin and tamoxifen on time to first recurrence<sup>1</sup>

Test for interaction between goserelin and tamoxifen  $p=0.025$ .

Abbreviations: CI, confidence interval.

<sup>1</sup>First of: disease recurrence, contralateral breast cancer, other cancer or death without a reported recurrence.

<sup>2</sup>Comparison of goserelin given versus goserelin not given (reference), controlling for tamoxifen.

<sup>3</sup>Comparison of tamoxifen given versus tamoxifen not given (reference), controlling for goserelin.

<sup>4</sup>Likelihood-ratio test.



## **Legend**

### **Figure 1.** Study design and flow diagram

All patients with breast conserving surgery were assigned radiotherapy (RT) to the breast, 50 Gy's in 5 weeks.

Abbreviations: pT: pathological tumour size, pN: pathological nodal status, CMF: cyclophosphamide, methotrexate and 5-fluorouracil. Tam: tamoxifen

## **Legend**

**Figure 2.** First event according to treatment groups

Abbreviations: C: controls, G: goserelin, T: tamoxifen, TG: tamoxifen and goserelin, G-: without goserelin, G+: with goserelin, T-: without tamoxifen, T+: with tamoxifen

## Legend

**Figure 3.** Effect of goserelin and tamoxifen treatment on time to event.

## Legend

### Figure 4. Subpopulation treatment effect pattern plot at different ER levels

The curves show hazard ratios on a logarithmic scale for treatment interactions. Circles represent the treatment effect (plotted at the category mean) in the ER categories:  $<0.05$ ,  $0.05$ - $0.59$  and  $\geq 60$  fmol/ $\mu$ g DNA.

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**Table 1.** Baseline patient characteristics by allocated treatment

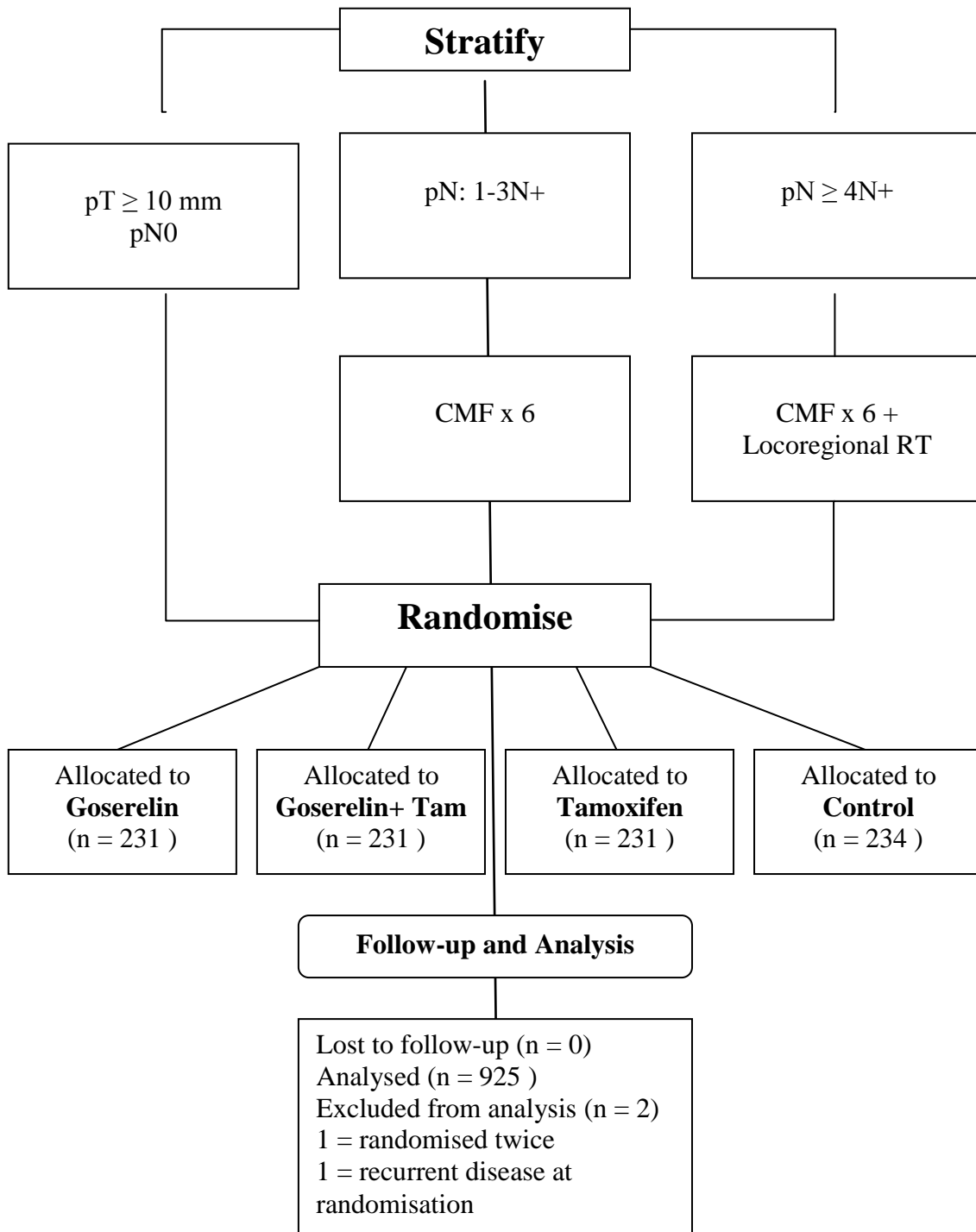
	Control N = 234	Goserelin N = 231	Tamoxifen N = 231	Goserelin & Tamoxifen N = 229
Age at randomisation (SD), years	45.4 (5.5)	46.0 (4.9)	45.6 (5.1)	45.5 (5.0)
Histopathological nodal involvement				
N0	116 (50%)	118 (51%)	117 (51%)	114 (50%)
N1-3	81 (35%)	80 (35%)	79 (34%)	79 (35%)
N4+	37 (16%)	33 (14%)	35 (15%)	36 (16%)
Histopathological tumour size (mm)				
≤20	152 (65%)	149 (65%)	153 (66%)	139 (61%)
21-50	73 (31%)	74 (32%)	72 (31%)	82 (36%)
>50	5 (2%)	4 (2%)	4 (2%)	4 (2%)
Unavailable	4 (2%)	4 (2%)	2 (1%)	4 (2%)
Estrogen receptor status				
Positive <sup>1</sup>	151 (65%)	147 (64%)	153 (66%)	141 (62%)
Negative <sup>2</sup>	51 (22%)	44 (19%)	50 (22%)	56 (25%)
Unavailable	32 (13%)	40 (17%)	28 (12%)	32 (14%)
Scheduled for chemotherapy	118 (50)	113 (49)	114 (49)	114 (50)

**Table 2.** Effects of goserelin and tamoxifen on time to first recurrence<sup>1</sup>

Analyses	Hazard rate ratio (95% CI)	P-value <sup>4</sup>
<u>Effect of endocrine treatment:</u>		
No endocrine therapy	1 (reference)	
Goserelin alone	0.68 (0.52 to 0.89)	0.021
Tamoxifen alone	0.73 (0.56 to 0.94)	
Both goserelin and tamoxifen	0.76 (0.59 to 0.98)	
<u>Effect of Goserelin:</u>		
Main effect <sup>2</sup>	0.84 (0.68 to 1.02)	0.07
Effect in women treated with tamoxifen	1.05 (0.80 to 1.38)	0.72
Effect in women <u>not</u> treated with tamoxifen	0.68 (0.53 to 0.89)	0.005
<u>Effect of Tamoxifen:</u>		
Main effect <sup>3</sup> :	0.89 (0.74 to 1.08)	0.24
Effect in women treated with goserelin	1.12 (0.85 to 1.47)	0.42
Effect in women <u>not</u> treated with goserelin	0.73 (0.56 to 0.95)	0.018

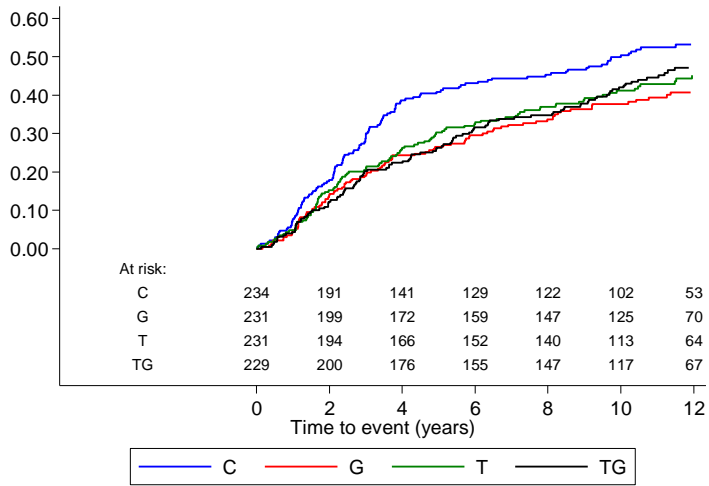


**Figure 1. Study design and flow diagram**

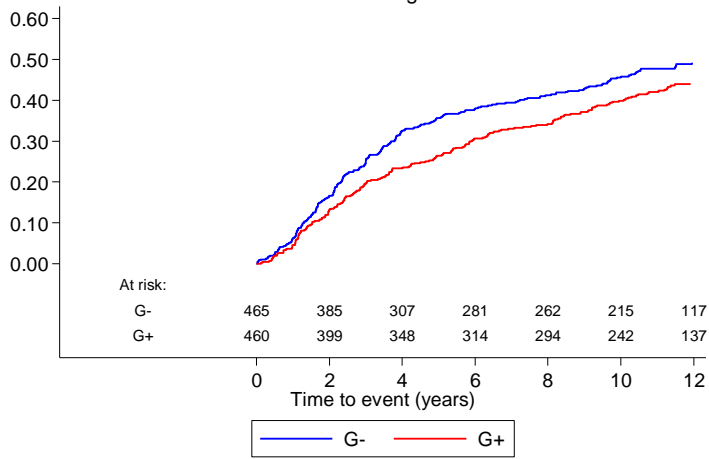


**Figure 2.** First event according to treatment groups

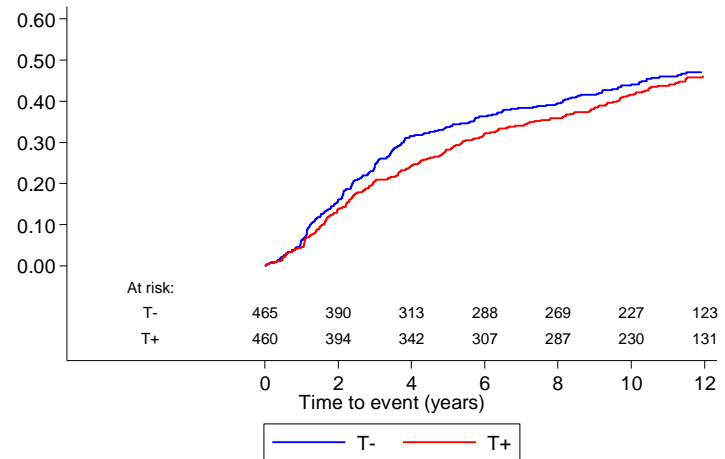
ZIPP STOCKHOLM

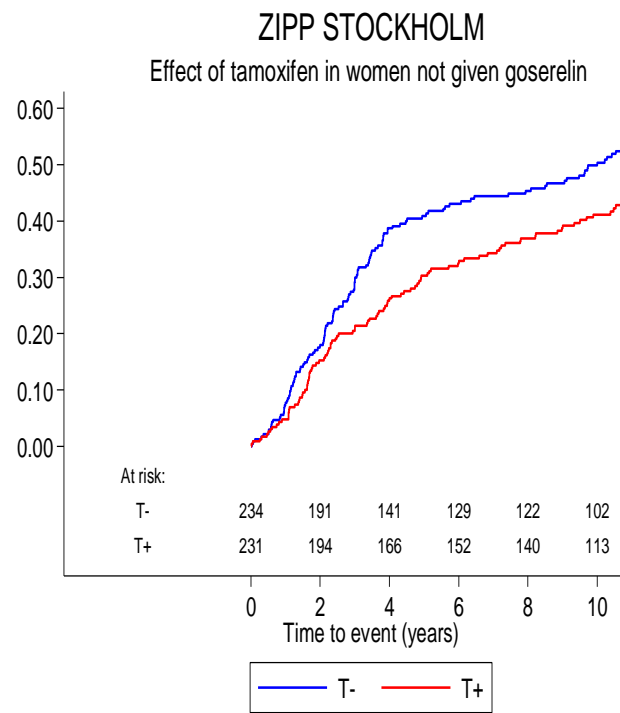
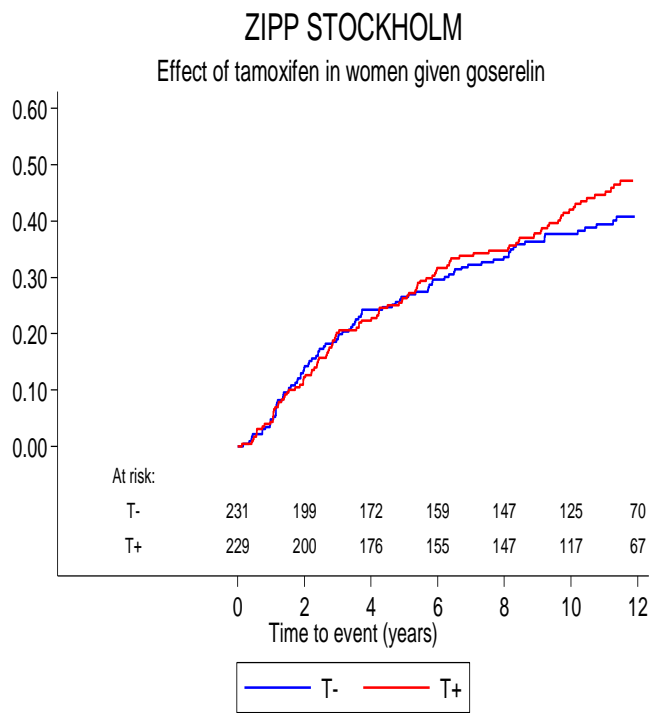


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Main effect of goserelin



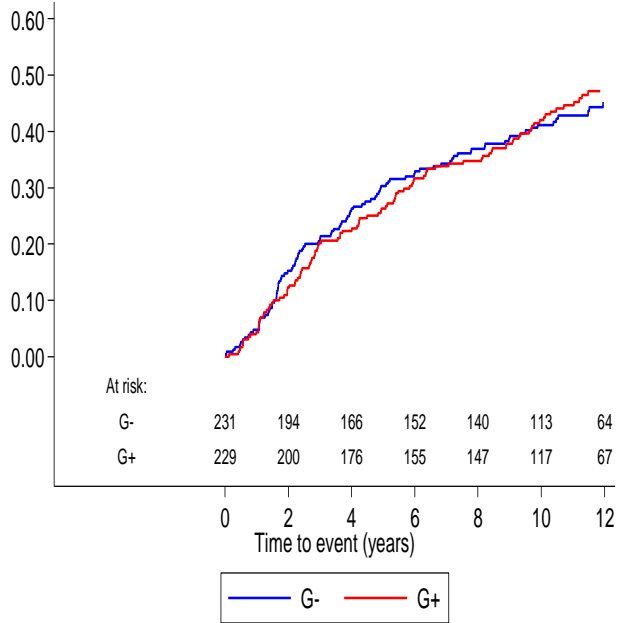
ZIPP STOCKHOLM  
Main effect of tamoxifen





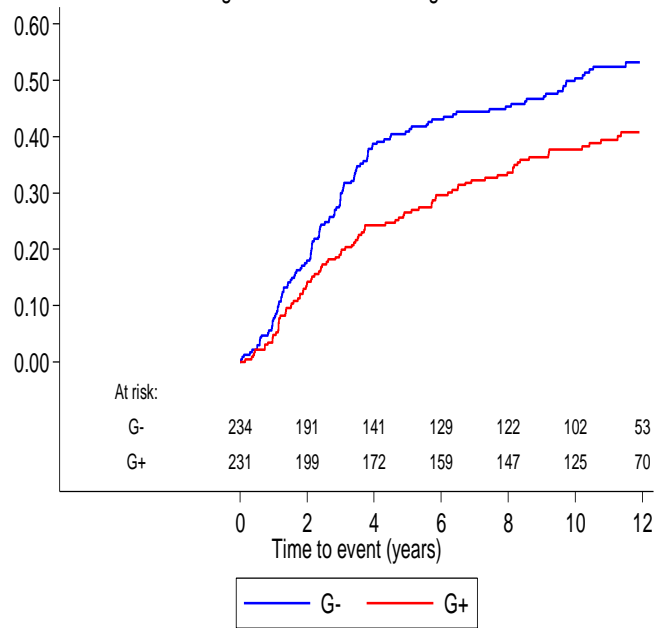
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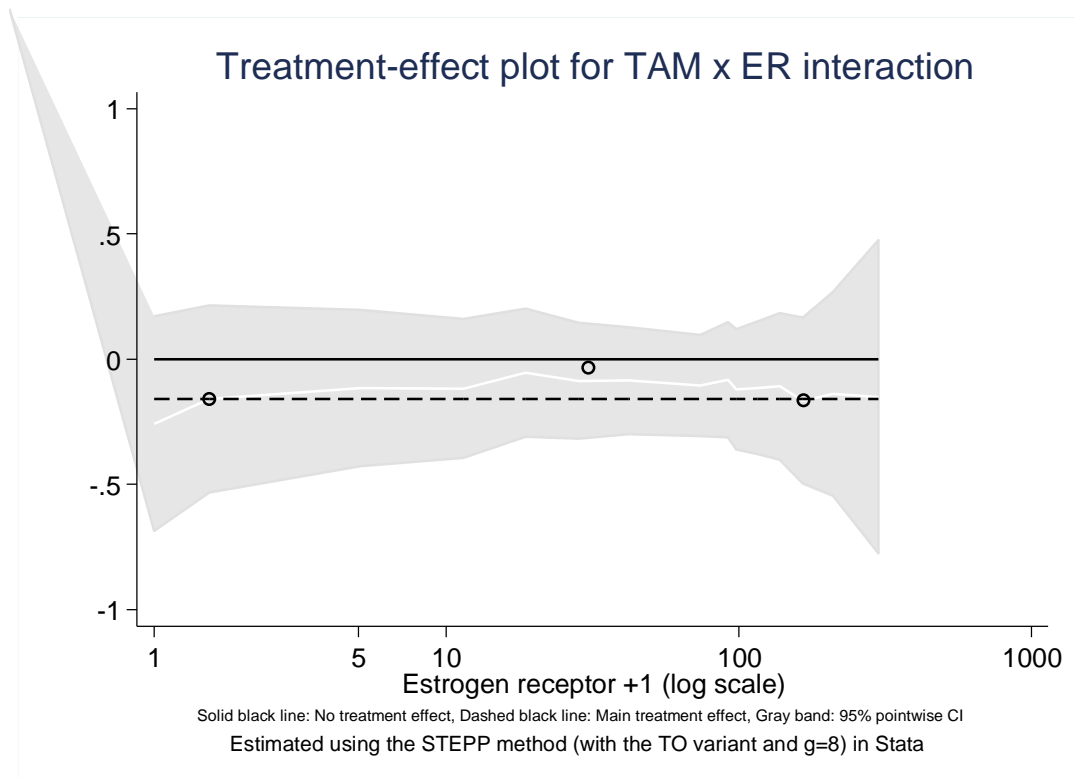
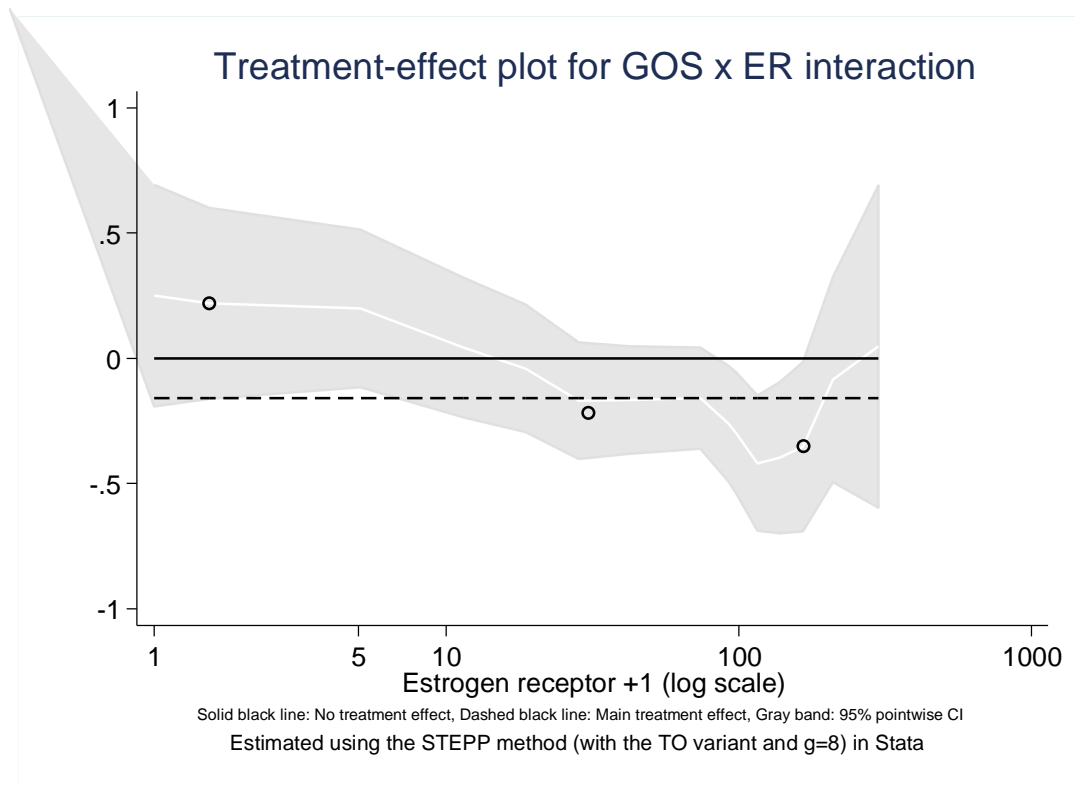
Effect of goserelin in women given tamoxifen



### ZIPP STOCKHOLM

Effect of goserelin in women not given tamoxifen





The curves show hazard ratios on a logarithmic scale for treatment ER interactions. Circles represents the treatment effect (plotted at the category mean) in the ER-categories: <0.05, 0.05-0.59 and  $\geq 0.60_{\text{fmol}}/\mu\text{g}/\text{DNA}$ .