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Adjuvant goserelin in pre-menopausal patients with early breast cancer: Results from the ZIPP study

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ABSTRACT

The Zoladex In Pre-menopausal Patients (ZIPP) study was designed to determine whether addition of goserelin ('Zoladex') and/or tamoxifen to adjuvant therapy (radiotherapy and/or chemotherapy), provided benefit to pre- or peri-menopausal women with operable, early breast cancer. A combined analysis of four randomised trials using a core protocol was performed. Patients ($n = 2710$) were randomised into a 2×2 factorial trial based on goserelin and tamoxifen ($n = 1800$) or randomised to receive goserelin or not ($n = 910$; some received elective tamoxifen) for 2 years. The analysis presented here compares women who did ($n = 1354$) or did not ($n = 1356$) receive goserelin. After a median follow-up of 5.5 years, goserelin provided a significant benefit for event-free survival (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.69, 0.92; $P = 0.002$) and overall survival (HR 0.81; 95% CI 0.67, 0.99; $P = 0.038$). Goserelin was well tolerated. These data show that the addition of goserelin to standard adjuvant therapy is more effective than standard therapy alone in pre-menopausal women with early breast cancer.

1. Introduction

An overwhelming body of evidence indicates that oestrogen plays a fundamental role in the pathogenesis of breast cancer. The risk of developing breast cancer appears to be associated with a number of factors related to the level and the length of exposure to oestrogen.[1,2] The obvious method to reduce the concentration of circulating oestrogen is surgical removal or irradiation of the ovaries but more recently medical castration with luteinising hormone-releasing hormone (LHRH) agonists has been introduced. In the first international overview, a significant advantage was observed for ovarian ablation, although oncologists (and patients) were still unable to agree if the benefits outweighed the disadvantages (for example, immediate menopausal symptoms such as hot flushes, night sweats and the long-term results of premature

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menopause).[3] The most recent published international overview of ovarian ablation[4] indicated that women under the age of 50 treated with ovarian ablation had an annual odds reduction in recurrence (25%) and mortality (24%); benefits that are similar to those obtained in patients who receive adjuvant chemotherapy. The effect was mainly limited to patients who were oestrogen receptor (ER) positive. Data from the overview suggest that ovarian ablation has a somewhat smaller effect (about 10% less) in the presence of chemotherapy than in its absence, possibly because the chemotherapy itself (particularly cyclophosphamide) exerts a chemical ablative effect. To achieve maximum effect chemotherapy regimens need to induce a permanent cessation of menses,[3] this would therefore have the same long-term effect on bone mineral density as surgical castration. In theory, a limited course of a GnRH (Gonadotropin releasing hormone) analogue might be associated with a smaller risk of osteoporotic fractures later in the patient's life should menses be re-established. Both node-positive and node-negative patients benefit from ovarian ablation, and mortality from causes other than breast cancer is not increased. The latter is a particularly important observation since menopause is associated with other adverse health outcomes, especially increased risk of cardiovascular disease and osteoporosis.

LHRH analogues act on the hypothalamic pituitary gonadal axis and inhibit (tachphylaxis) secretion of pituitary gonadotrophins, leading to decreased production of oestradiol from the ovaries (to post-menopausal levels). The most intensively investigated LHRH agonist is goserelin ('Zoladex'), now an established therapy for the management of advanced breast cancer in both pre- and peri-menopausal women. A total of 29 studies (228 patients enrolled) in advanced disease showed a response rate of 36% (median response duration 44 weeks).[3] These results are comparable with those obtained with conventional ovarian ablation, and tamoxifen, in similar groups of patients.[3] The responses to goserelin were achieved regardless of patient age, tumour grade, previous hormone therapy, disease site, or ER status (although higher response rates were seen in ER-positive and/or well-differentiated tumours). Goserelin could therefore, be an important adjuvant treatment for early breast cancer and this paper reports the results of the largest trial so far performed in this setting.

The ZIPP trial (Zoladex in Pre-menopausal Patients) was an international collaboration between four trial groups: the British Cancer Research Campaign (CRC – now Cancer Research UK [CRUK]) Breast Cancer Trials Group (BCTG), the Stockholm Breast Cancer Trials Group, the South East (SE) Sweden Breast Group and the Italian GIVIO collaborative group. Each of the four collaborative groups ran a trial of similar design based on a core protocol designed to allow for an eventual meta-analysis to be carried out. It was designed to determine whether goserelin with or without tamoxifen offered any additional benefit to standard therapy in the management of pre-menopausal breast cancer, as determined at local centres. This can be described as a 'pragmatic design' to allow the results obtained to be applicable to a broad cross-section of clinical practice. Tamoxifen was included as a main factor because at the time the trials were established, there was uncertainty over its effectiveness in pre-menopausal women. However, tamoxifen has since been shown to be effective, or in other words, that arm of the factorial design has been overtaken by events. For this reason we concentrate on the results associated with the effect of goserelin, but still present some results according to each of the four treatment arms. The tamoxifen data continues to be incorporated into the EBCTCG overviews.

2. Patients and methods

2.1. Study design

The ZIPP collaboration includes four unblinded, randomised, multicentre trials conducted in women who were pre-menopausal or aged under 50 years with operable stage I or II breast cancer, regardless of ER status. This study was designed prospectively by using a core protocol, which each collaborative group adapted according to local requirements (Table 1 shows selected characteristics). At the time of trial design (1985) ER status was not routinely recorded among European patients. However, it became known subsequently that many ER negative cases were included in the study, providing an internal check on the plausibility of the results and emphasising the importance of routine measurement of this biological predictive factor.

Local treatment (surgery with or without radiotherapy) and adjuvant chemotherapy (where appropriate) were planned according to local treatment policies prior to randomisation. Patients in the Stockholm and GIVIO trials were included in a 2×2 factorial randomisation to goserelin (3.6 mg subcutaneous depot injection into the abdominal wall every 4 weeks), tamoxifen (20 or 40 mg daily), combination of goserelin and tamoxifen or no endocrine treatment for 2 years. Patients in the CRUK and SE Sweden trials were initially randomised into the four arms, but with the publication of the data on tamoxifen in younger patients[3] investigators were permitted to give tamoxifen electively, followed by randomisation to goserelin or no goserelin (Fig. 1).

2.2. Patient population

Patients were entered into the trial following primary therapy, which included surgery (local excision or mastectomy), and post-operative radiotherapy and adjuvant systemic chemotherapy, where appropriate. Patients were selected for chemotherapy according to local criteria (mainly those at a higher risk of recurrence due to the presence of involved nodes) and the type given was also determined locally (peri-operative cyclophosphamide or six cycles of cyclophosphamide/methotrexate/5-fluorouracil [CMF] chemotherapy were recommended in the protocol but some centres used a standard 5-fluorouracil/epirubicin/cyclophosphamide regimen).

For inclusion into the trial, patients were required to be less than 50 years of age at the time of randomisation (or pre-menopausal in the Stockholm trial and in some centres in the CRUK trials) with invasive, operable breast cancer, confined to one breast; to have no evidence of distant metastases following X-ray of chest, spine and pelvis; and to have normal liver and renal function tests and normal full blood counts (neutrophils $\geqslant3\times10^9$/l; platelets $\geqslant90\times10^9$/l; haemoglobin $\geqslant10$ g/dl).

Patients were excluded from the study if they had received hormonal therapy within the 6 weeks prior to joining

Table 1 – Summary of the patient populations in the ZIPP subtrials

	Period of recruitment	Patient population	Elective treatment(s)[1]	Randomised treatment(s)[2]
CRUK BCTG	August 1987–March 1999	<50 years or pre-menopausal Operable, stage I or II Any nodal or ER status	Up to six cycles of chemotherapy for high-risk patients	Initially all patients entered into 2 × 2 randomisation, from February 1991, tamoxifen randomisation optional/elective tamoxifen allowed Tamoxifen 20 mg daily
Stockholm	May 1990–January 1997	<50 years or pre-menopausal Operable breast cancer of >10 mm in size or node-positive	All patients had conservative surgery Node-positive patients received six cycles of CMF	All patients entered into 2 × 2 randomisation Tamoxifen 40 mg daily
SE Sweden	October 1989–March 1998	<50 years, regardless of nodal or menopausal status Operable stage I or II disease	Combination chemotherapy for high-risk patients	All patients entered into 2 × 2 randomisation Tamoxifen 40 mg daily From November 1991 all patients given tamoxifen
GIVIO	January 1991–November 1996	<50 years, regardless of nodal, ER or menopausal status Operable stage I or II disease	Up to six cycles of chemotherapy for high-risk patients	All patients entered into 2 × 2 randomisation Tamoxifen 20 mg daily

1 All patients in all trials had local therapy prior to randomisation (surgery +/− radiotherapy) according to institutional treatment policies.
2 Randomised Zoladex was 3.6 mg depot every 4 weeks for 2 years.

the trial; if they were unfit for surgery (or radiotherapy, if relevant) or if they had a severely limited life expectancy as a result of intercurrent illness; if they had previously received treatment for other malignancies (with the exception of basal or squamous cell carcinoma of the skin or adequately biopsied in situ carcinoma of the cervix); or if the primary carcinoma was fixed to the underlying muscle or chest wall or was ulcerated, had skin infiltration or axillary nodes that demonstrated deep fixity were present. Patients unwilling or unable to attend for treatment and long-term follow-up were also excluded.

Entry of patients to each trial was by the local clinician contacting the appropriate trials office. This contact was only made after surgery, when it was apparent that the patient complied with the inclusion and exclusion criteria. Clinical decisions as to whether an individual patient was to receive prophylactic irradiation, systemic chemotherapy and elective tamoxifen (after February 1991) had to be made prior to contacting the trials office. A checklist was completed before randomisation to confirm a patient's eligibility, and non-randomised treatments to be given were checked against previously defined policy statements for each centre. These statements were held on file in the trials office and ensured that the delivering of other treatments did not confound the allocation of trial therapy.

Patients were asked to begin treatment as soon as possible after surgery. Tamoxifen was administered orally (20 or 40 mg daily) and goserelin (3.6 mg every 28 days) was given as a subcutaneous injection into the abdominal wall. Randomised therapy continued for 2 years unless a treatment endpoint was reached, treatment was stopped due to adverse events or a patient withdrew. Patients suffering menopausal symptoms were allowed concomitant hormone replacement therapy, but this had to be notified to the trials office.

Follow-up was carried out according to local protocols, but reports on each patient were required for trial analysis at a minimum of every 6 months for the initial 2 years while the patient was on trial therapy, and then at least annually. Reports of recurrent disease and new malignancies required biopsy and/or appropriate imaging for confirmation. Follow-up continued for all patients who withdrew from therapy.

The ZIPP trial was designed and conducted in accordance with the Declaration of Helsinki 1975 (as amended by the 35th World Medical Assembly, Venice, 1983). The ethics committee of each centre taking part in the trial approved the protocol and it was the responsibility of each investigator to obtain informed consent from patients in the manner recommended by the local ethics committee.

2.3. *Statistical methodology*

By combining the four trials in a meta-analysis based on about 2700 patients, an absolute difference in 5-year survival of 5% (from 70% in the control group to 75% in the treated group) could be detected with 83% power. Each collaborative group collected data for their own patients. A list of variables and their definitions were agreed and the data from each trial was supplied to the CRUK BCTG for analysis.

All analyses were performed on an 'intention to treat' basis and were associated with the main effect analysis of goserelin

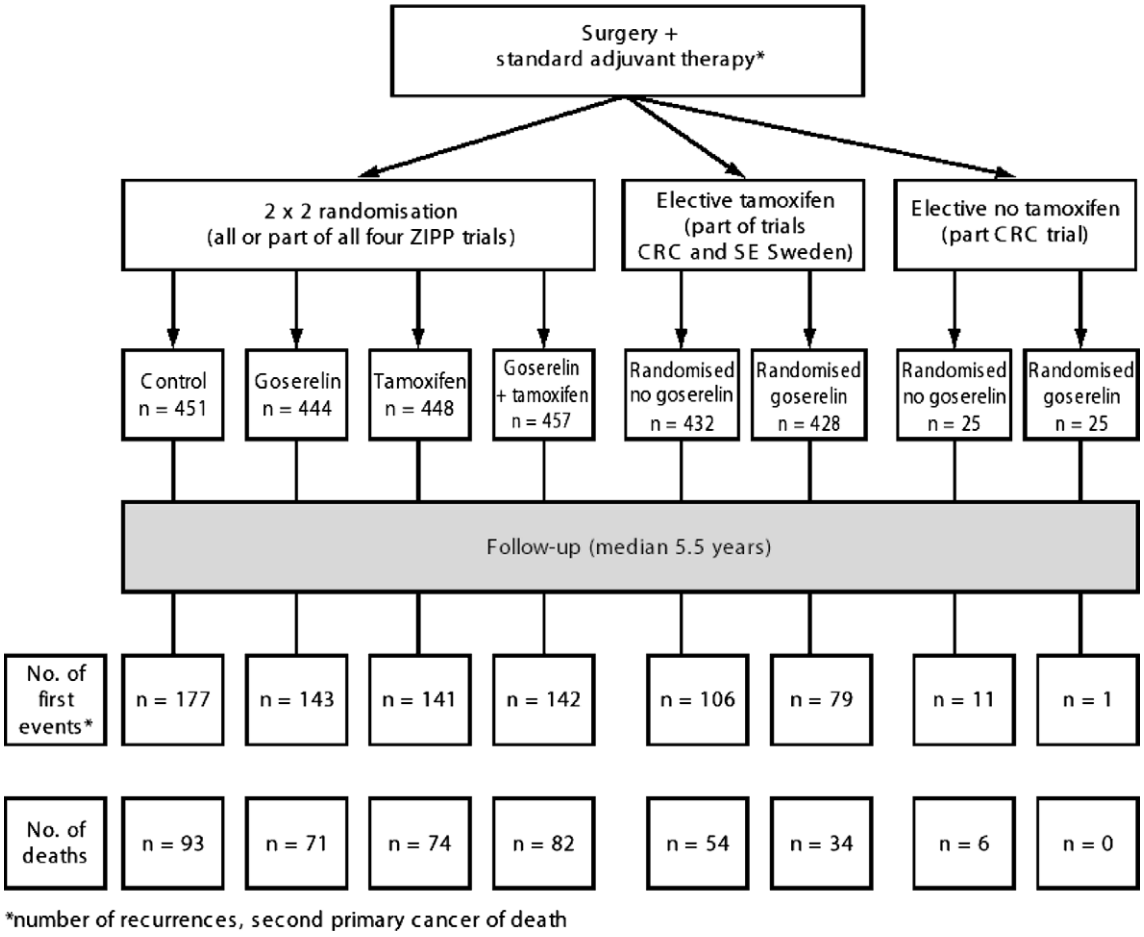


Fig. 1 – The distribution of patients in the ZIPP trial and the number of events according to the different treatment arms.

versus no goserelin. Event-free survival (EFS) was defined as the interval from randomisation to the date of first confirmed recurrence (local or distant), second primary cancer or death. If none of these events occurred, EFS was censored at the date of last follow-up. Overall survival was defined as the interval from randomisation to the date of death. Results were presented as hazard ratios (HR) with 95% confidence intervals (CI) after allowing for stratification by the four trials. Prespecified subgroup analyses for various prognostic and treatment factors were also performed (node status, hormone receptor status, use of adjuvant chemotherapy).

2.4. *Tolerability*

Analyses of tolerability (side-effects) were not part of the ZIPP meta-analysis, but limited data from the largest trial (CRUK) are reported here and data on side-effects have already been reported for the Stockholm trial.[5]

3. Results

3.1. *Patients*

Between August 1987 and March 1999, a total of 2710 patients were recruited from the four trial groups (CRUK BCTG, $n = 1191$; Stockholm, $n = 926$; SE Sweden, $n = 211$ and GIVIO, $n = 382$). Fig. 1 shows the distribution of patients between the various treatment arms. The 50 patients (from the CRUK trial) who, as an elective decision, did not receive tamoxifen, were all given adjuvant systemic chemotherapy in accordance with that centre's policy.

Overall, baseline characteristics were well balanced between patients who did and did not receive goserelin and were similar between the four trial groups (Table 2).

3.2. *Efficacy*

After a median follow-up of 5.5 years, 365 patients (27%) randomised to goserelin were reported to have experienced a first event compared with 435 patients (32%) in the control group (Table 3). Goserelin was associated with a statistically significant 20% reduction in the risk of having an event (first recurrence, second primary cancer or death) compared with patients who did not receive goserelin (HR for EFS was 0.80; 95% CI 0.69–0.92; $P = 0.002$ [Fig. 2]). The absolute difference in EFS between the groups at 5 years was 5.2% (goserelin 74.6% and control 69.4%). There was also a statistically significant benefit for overall survival. Women given goserelin had a 19% reduction in the risk of dying compared to those not given goserelin (HR for overall survival was 0.81;

Table 2 – Patient characteristics by randomised treatment group and subtrial

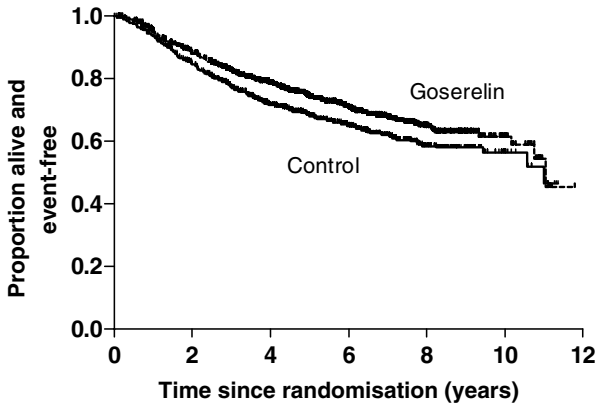
	Number of patients (%)					
	Goserelin (*n* = 1354)	Control (*n* = 1356)	CRUK BCTG (*n* = 1191)	Stockholm (*n* = 926)	GIVIO (*n* = 382)	SE Sweden (*n* = 211)
Age (years)						
Median	44	44	43	46	44	44
Range	22–56	21–55	22–53	26–56	21–50	23–49
Distribution						
⩽39	280 (21)	326 (24)	352 (30)	126 (14)	85 (22)	43 (20)
>40	1074 (79)	1030 (76)	839 (70)	800 (86)	297 (78)	168 (80)
Menopausal status						
Pre-menopausal	979 (72)	967 (71)	760 (64)	903 (97)	283 (74)	NR
Post-menopausal	78 (6)	72 (5)	108 (9)	7 (1)	35 (9)	NR
Unknown	297 (22)	317 (24)	323 (27)	16 (2)	64 (17)	211 (100)
Tumour size						
⩽10 mm	148 (11)	159 (12)	180 (15)	74 (8)	40 (10)	13 (6)
11–20 mm	604 (45)	603 (44)	445 (37)	519 (56)	159 (42)	84 (40)
21–50 mm	454 (33)	449 (33)	367 (31)	300 (32)	131 (34)	105 (50)
>50 mm	28 (2)	38 (3)	30 (3)	17 (2)	12 (3)	7 (3)
Unknown	120 (9)	107 (8)	169 (14)	16 (2)	40 (11)	2 (1)
Oestrogen receptor status						
Positive	672 (50)	713 (53)	446 (37)	591 (64)	195 (51)	153 (72)
Negative	335 (25)	312 (23)	296 (25)	201 (22)	108 (28)	42 (20)
Unknown	347 (26)	331 (24)	449 (38)	134 (14)	79 (21)	16 (8)
Positive nodes						
Negative	722 (53)	713 (53)	720 (60)	464 (50)	187 (49)	64 (30)
Positive	558 (41)	571 (42)	326 (28)	462 (50)	194 (51)	147 (70)
Unknown	74 (5)	72 (5)	145 (12)	0	1 (<1)	0
Surgery						
Local excision	675 (50)	696 (51)	681 (57)	436 (47)	164 (43)	90 (43)
Mastectomy	663 (49)	651 (48)	510 (43)	488 (53)	195 (51)	121 (57)
Unknown	16 (1)	9 (1)	0 (0)	2 (<1)	23 (6)	0 (0)
Radiotherapy						
Yes	817 (60)	870 (64)	822 (69)	541 (58)	135 (35)	189 (90)
No	507 (38)	462 (34)	355 (30)	383 (41)	209 (55)	22 (10)
Unknown	30 (2)	24 (2)	14 (1)	2 (<1)	38 (10)	0 (0)
Chemotherapy						
Yes	583 (43)	590 (44)	439 (37)	459 (50)	232 (61)	43 (20)
No	766 (56)	761 (56)	742 (62)	467 (50)	150 (39)	168 (80)
Unknown	5 (<1)	5 (<1)	10 (<1)	0 (0)	0 (0)	0 (0)
Median duration of follow-up (years)	5.5	5.6	5.0	6.0	5.2	5.7

NR, not recorded.

Table 3 – First events according to treatment

	Number of patients[a] (%)	
	Goserelin (n = 1354)	Control (n = 1356)
Disease recurrence		
Local	138 (10)	186 (14)
Distant	173 (13)	191 (14)
Unknown site	3 (<1)	2 (<0.1)
Second primary tumour		
Contralateral breast	32 (2)	43 (3)
Other	21 (2)	19 (1)
Death without recurrence	17 (1)	17 (1)
Total	365 (27)	435 (32)

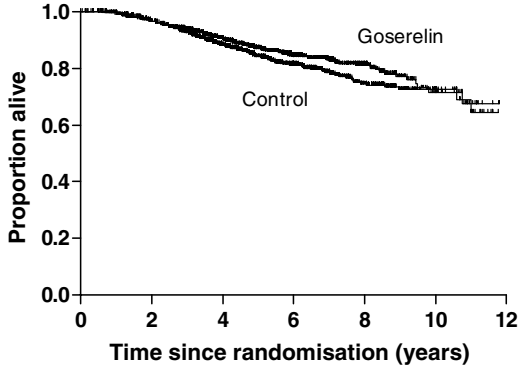
a Patients may appear in more than one category.



Number at risk:

No goserelin	1356	1062	702	381	134	22	0
Goserelin	1354	1108	772	418	156	31	0

Fig. 2 – Kaplan–Meier curve of event-free survival in patients receiving goserelin or no goserelin in addition to standard adjuvant therapy.



Number at risk:

No goserelin	1356	1216	877	486	178	33	0
Goserelin	1354	1214	893	501	198	37	0

Fig. 3 – Kaplan–Meier curve of overall survival in patients receiving goserelin or no goserelin in addition to standard adjuvant therapy.

95% CI 0.67–0.99, P = 0.038 [Fig. 3]). In the analysis of survival, a total of 187 (14%) patients randomised to goserelin had died by the time of analysis, compared with 227 (17%) in the control group. The majority of deaths were from breast cancer, with 154 (82% of all deaths) versus 174 (77% of all deaths) patients dying in the goserelin and control groups, respectively. The absolute difference in overall survival at 5 years was 2.7% (goserelin 87.6% and control 84.9%).

For completeness, we also examined the effect of tamoxifen on survival. The hazard ratio for EFS was 0.79 (95% CI 0.68–0.92) and for overall survival it was 0.83 (95% CI 0.68–1.02); consistent with expectation.

The HRs for EFS and overall survival were broadly similar between the four trials (Table 4). A test for heterogeneity between the HR was not statistically significant (EFS, P = 0.08; overall survival; P = 0.14). Although the estimate of the HR was raised in the GIVIO trial, it was not statistically significant (HR 1.29, P = 0.20), and the results from the two largest trials showed a clear benefit.

New tumours (as a first event) were reported in 53 patients in the goserelin group and 62 patients in the control group (Table 3). Of these, 75 were contralateral breast cancers; 32 in the goserelin group and 43 in the control group. There was some evidence of a reduction in the incidence of contralateral breast cancer (as a first event) for patients receiving goserelin, although this was not statistically significant; relative risk 0.75 (95% CI 0.47–1.17, P = 0.24). Results on the risk of contralateral breast cancer in each treatment arm were as follows: no tamoxifen or goserelin (13/476 patients, relative risk 1.0); tamoxifen only (30/880 patients, relative risk 1.25 95% CI 0.66–2.37); goserelin only (12/469, relative risk 0.94 95% CI 0.43–2.03); tamoxifen plus goserelin (20/885, relative risk 0.83 95% CI 0.42–1.65).

Subgroup analyses for EFS and overall survival were carried out based upon prognostic and treatment factors. The analyses for nodal status, receptor status and adjuvant chemotherapy were agreed at the time the trial was designed, but the analyses by age was not. Table 4 shows the HRs and 95% CIs for each of the subgroups. There was an indication that goserelin was more effective in women who were node-negative, ER-positive and had not received chemotherapy, though a test for heterogeneity was not statistically significant for each factor, probably because of limited statistical power. An exploratory analysis of the interactions of chemotherapy with goserelin according to ER status was performed (Table 5). In this analysis, ER-positive patients who had not received chemotherapy appeared to derive more benefit from goserelin (HR 0.68) than other patients. However, ER-positive patients who received chemotherapy still derived some benefit from goserelin (HR 0.83). Similarly, ER-negative patients who had not received chemotherapy, also appeared to derive some benefit (HR 0.79), while ER-negative patients who had received chemotherapy do not derive any benefit from goserelin (HR 1.19). The results arising from the subgroup analyses were not statistically significant and although they may be suggestive of different effects among different groups of women they do not provide sufficient evidence for this.

We also explored the separate effects of tamoxifen and goserelin and their interaction on the chance of overall survival (Table 6 and Fig. 4). Compared to women who received

Table 4 – Hazard ratios for event-free survival and overall survival according to trial and specified subgroups

	Number of patients	Event-free survival		Overall survival	
		Number of events	Hazard ratio (95% CI)	Number of events	Hazard ratio (95% CI)
Trial					
CRUK	1191	327	0.68 (0.55–0.85)	179	0.67 (0.50–0.90)
Stockholm	926	309	0.78 (0.62–0.97)	155	0.84 (0.61–1.15)
Sweden	211	61	0.94 (0.56–1.55)	35	0.80 (0.41–1.55)
GIVIO	382	103	1.29 (0.87–1.90)	45	1.64 (0.90–2.99)
Age (years)					
<40	606	226	0.87 (0.67–1.14)	124	0.76 (0.53–1.09)
⩾40	2104	574	0.79 (0.67–0.93)	290	0.86 (0.68–1.08)
Nodes					
Negative (no nodes)	1435	339	0.69 (0.56–0.86)	140	0.80 (0.58–1.12)
Positive (⩾1 node)	1129	418	0.92 (0.76–1.11)	250	0.82 (0.64–1.06)
Unknown	146	43	0.72 (0.39–1.32)	24	0.75 (0.34–1.68)
ER status					
Negative	647	244	0.94 (0.73–1.21)	152	0.89 (0.64–1.22)
Positive	1385	397	0.75 (0.61–0.92)	185	0.79 (0.59–1.06)
Unknown	678	159	0.73 (0.53–1.00)	77	0.74 (0.47–1.16)
Chemotherapy					
Received	1173	388	0.87 (0.72–1.07)	225	0.78 (0.60–1.02)
Not received	1527	407	0.74 (0.61–0.90)	185	0.88 (0.66–1.17)
All women	2710	800	0.80 (0.69–0.92)	414	0.81 (0.67–0.99)

Table 5 – Analysis of survival data according to ER status and whether chemotherapy was received or not

	Number of patients	Event-free survival		Overall survival	
		Number of events	Hazard ratio (95% CI)	Number of events	Hazard ratio (95% CI)
ER−ve					
No chemotherapy	342	123	0.79 (0.56–1.13)	70	0.77 (0.48–1.24)
Chemotherapy	303	120	1.19 (0.83–1.71)	81	1.09 (0.70–1.70)
ER +ve					
No chemotherapy	829	206	0.68 (0.51–0.90)	83	0.80 (0.52–1.24)
Chemotherapy	554	190	0.83 (0.62–1.10)	101	0.77 (0.52–1.14)

neither tamoxifen nor goserelin (the control group), those who took either treatment or both had a similar hazard ratio. There was insufficient evidence to suggest that taking both treatments had the greatest effect; a test for an interaction between tamoxifen and goserelin was not statistically significant ($P = 0.25$). The effect was similar in women aged 40 years and over, though in younger women the results were less conclusive because of the smaller number of events (the 95% confidence intervals were somewhat wide and included one).

3.3. *Tolerability*

Data on safety for the CRUK trial are shown in Table 7. The proportion of patients who reported at least one side-effect was lowest (18%) in the control group and greatest in the combination group (65%). The most common event was hot flushes, reported by 78 (17%) patients treated with tamoxifen alone, 35 (26%) patients treated with goserelin alone, and 200 (44%) patients treated with both tamoxifen and goserelin. Patients receiving no adjuvant endocrine therapy did not report hot flushes. The only other side-effect with more than 50 reports was weight gain. The incidence was higher in the combination group (11%) than either of the other two hormonal groups (tamoxifen alone 7%; goserelin alone 4%) or in the control group (0%) (Table 7).

4. Discussion

This combined analysis of four randomised trials represents the largest study examining the role of goserelin in the adjuvant treatment of early breast cancer. Indeed, the analysis encompasses a greater number of patients than the EBCTCG overview ($n = 2102$),[4] or in any other trial of adjuvant goserelin in this setting.

The efficacy data from this trial show that addition of goserelin to standard adjuvant therapy results in a prolongation of event-free survival and overall survival in pre/perimenopausal women with operable breast cancer. When the trial was initiated there was no undisputable evidence on the role of ER but this is now the only subgroup that would

Table 6 – The effect on overall survival for each of the four treatment groups, and according to specified factor

	Control[a]		Tamoxifen only		Goserelin only		Both tamoxifen and goserelin	
	Number of deaths/ number of patients	Hazard ratio	Number of deaths/ number of patients	Hazard ratio (95% CI)	Number of deaths/number of patients	Hazard ratio (95% CI)	Number of deaths/ number of patients	Hazard ratio (95% CI)
Age (years)								
<40 years	23/112	1.00	51/214	1.31 (0.79–2.17)	15/79	0.89 (0.46–1.70)	35/201	0.92 (0.54–1.58)
40+ years	76/364	1.00	77/666	0.59 (0.42–0.82)	56/390	0.67 (0.48–0.95)	81/684	0.61 (0.44–0.84)
Nodal status								
Negative (no nodes)	35/228	1.00	42/485	0.58 (0.36–0.92)	29/236	0.78 (0.48–1.28)	34/486	0.47 (0.28–0.76)
Positive (≥1 node)	57/227	1.00	80/344	0.96 (0.68–1.36)	39/212	0.71 (0.47–1.06)	74/346	0.87 (0.61–1.23)
ER status								
Negative	33/111	1.00	45/201	0.79 (0.50–1.25)	27/109	0.85 (0.51–1.41)	47/226	0.73 (0.46–1.15)
Positive	45/246	1.00	60/467	0.78 (0.52–1.17)	31/239	0.72 (0.45–1.13)	49/433	0.66 (0.44–1.01)
Chemotherapy								
Not received	47/244	1.00	51/517	0.51 (0.34–0.77)	32/239	0.67 (0.43–1.06)	55/527	0.54 (0.36–0.81)
Received	52/232	1.00	74/358	0.98 (0.68–1.41)	39/228	0.74 (0.49–1.13)	60/355	0.79 (0.54–1.16)
All patients	99/476	1.00	128/880	0.75 (0.57–0.98)	71/469	0.71 (0.52–0.96)	116/885	0.67 (0.51–0.88)

a No tamoxifen or goserelin.

Fig. 4 – Kaplan–Meier curve of overall survival in patients receiving control, tamoxifen only, goserelin only or both tamoxifen and goserelin, in addition to standard adjuvant therapy.

be offered endocrine manipulation. A higher proportion of patients on chemotherapy would have been amenorrhoeic compared with those not receiving this therapy and therefore the benefit of further ovarian ablation was limited. Goserelin therefore offers an alternative adjuvant treatment for patients with pre-menopausal breast cancer as it reduces the risk of relapse and prolongs survival. Of particular importance, this trial allowed for the evaluation of goserelin against the background of other adjuvant treatments commonly employed in the management of pre-menopausal early breast cancer.

The effect on survival was similar in patients who received tamoxifen only and those receiving goserelin only. There was insufficient evidence to conclude whether the effect of the two treatments combined was associated with a greater survival.

Data from the CRUK (Table 6) and Stockholm trials[5] demonstrated that goserelin is well tolerated. The most common adverse events included hot flushes, weight gain and vaginal dryness. It has been reported that these symptoms persist in patients receiving prior chemotherapy but are reversible in patients without prior chemotherapy.[5]

The results associated with comparing the effect of goserelin versus no goserelin can be directly compared with the International Breast Cancer Study Group (IBCSG) trial, which had a similar design. The IBCSG trial[6] randomised 1063 women to receive goserelin alone ($n = 346$), chemotherapy alone ($n = 360$) or both ($n = 357$). The HR for disease-free survival for chemotherapy plus goserelin versus chemotherapy alone was 0.80 (95% CI 0.57–1.11), similar to our estimate of 0.87 (95% CI 0.72–1.07) (Table 4; data restricted to women who received chemotherapy). This trial also found a similar effect in women who were ER-negative and positive (HR for chemotherapy plus goserelin versus chemotherapy alone was 0.75 among ER−ve and 0.80 among ER+ve), whereas our data suggests there could be a greater effect in ER-positive women (HR 0.83 among ER+ve compared to 1.19 among ER−ve). They also reported that goserelin was more effective in younger women (⩽39 years) than in women aged ⩾40 years (HR 0.50 versus 0.92), though the ZIPP trial did not (HR 0.87 versus 0.79).

Although other trials have looked at the effect of goserelin, they are not directly comparable to the ZIPP trial because of

Table 7 – Major (incidence >5%) reported side-effects in the CRUK trial

	Randomised treatment			
	Control N = 137	Goserelin alone N = 134	Tamoxifen alone N = 463	Goserelin + tamoxifen N = 457
Vasodilation	0 (0)	35 (26)	78 (17)	200 (44)
Weight gain	0 (0)	5 (4)	32 (7)	50 (11)
Tiredness	0 (0)	2 (1)	10 (2)	12 (3)
Headache	0 (0)	5 (4)	5 (1)	21 (5)
Pain	0 (0)	8 (6)	9 (2)	11 (3)
Nausea/vomiting	0 (0)	9 (7)	0 (0)	4 (<1)
Bone pain/arthralgia	2 (1)	6 (5)	4 (1)	11 (2)
Anxiety/depression/irritability	1 (<1)	8 (6)	10 (2)	26 (6)
Sweating	0 (0)	7 (5)	5 (1)	23 (5)
Total number of patients with at least one side-effect	25 (18)	75 (56)	189 (41)	297 (65)

different designs. In the US Intergroup trial (INT 0101)[11] of 1503 pre-menopausal women, all patients received chemotherapy and were allocated to one of 3 arms; control group, 5 years of either goserelin or goserelin plus tamoxifen (in the ZIPP trial only high-risk patients had chemotherapy). The results were consistent between the two trials; the hazard ratio for overall survival for goserelin versus control was 0.88 (95% CI 0.70–1.11) compared to 0.71 (95% CI 0.52–0.96) in the ZIPP trial (Table 6). For the comparison of tamoxifen plus goserelin versus goserelin the hazard ratio in the INT 0101 trial was 0.74 (95% CI 0.60–0.91) and 0.91 (95% CI 0.71–1.15) for disease-free and overall survival, respectively, consistent with those from ZIPP, 0.88 (95% CI 0.71–1.09) and 0.95 (95% CI 0.81–1.10), suggesting that there may be a benefit of adding tamoxifen to goserelin on disease-free survival but not overall survival.

The ZEBRA trial (Zoladex Early Breast cancer Research Association), based on pre- or peri-menopausal women with node-negative breast cancer, randomised 817 women to receive goserelin alone and 823 to adjuvant chemotherapy alone (CMF).[7] After a median follow-up of approximately 7 years, goserelin and chemotherapy had equivalent effects on both disease-free survival and overall survival among patients who were ER-positive (HR of 1.05, 95% CI 0.88–1.14, for disease-free survival, and 0.94, 95% CI 0.75–1.18, for overall survival). In patients who were ER-negative, goserelin was clearly worse (HR 1.83, 95% CI 1.33–2.52 for disease-free survival and 1.64, 95% CI 1.13–2.39 for overall survival), consistent with our data which suggests that patients with ER-negative or node-positive disease may perform worse on goserelin compared with chemotherapy. The explanation for the apparent response in the ER-negative patients may be due to the presence of non-detectable but low ER levels, false-negative results based on the ligand binding assay commonly used in the late 1980s or alternatively, may be due to a differential response in women with ER-negative/progesterone receptor (PgR)-positive disease compared with those with both ER-negative and PgR-negative disease.[8] The ZEBRA trial also demonstrated that while goserelin is equivalent to CMF treatment, a proportion of women treated with CMF do not achieve amenorrhoea.[7] The antitumour effect of CMF in this setting is thought to be associated with the induction of amenorrhoea, indicative of ovarian suppression,[9,10] and the lack of such a response may provide an opportunity that can be exploited by goserelin.

St. Gallen and National Institute of Health (NIH) Consensus Development Panel recommendations for the adjuvant management of breast cancer include ovarian ablation (or a LHRH agonist) in combination with tamoxifen for pre-menopausal women with ER-positive disease.[12,13] The St. Gallen Consensus was updated in 2005 although is as yet unpublished.

In conclusion, the benefit resulting from the addition of goserelin to standard adjuvant therapies for early breast cancer has been clearly demonstrated in this large combined study. As a result, goserelin represents an effective and well-tolerated addition to standard adjuvant therapies for the treatment of early breast cancer. Additional analyses and follow-up from the ZIPP study will provide further insight into the use of goserelin in combination with other adjuvant therapies for the treatment of pre-menopausal women with early breast cancer.

Conflict of interest statement

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