Systematic review of luteinising hormone-releasing hormone agonists in adjuvant therapy of early breast cancer

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Prepared by Sharma R, Hamilton A, Beith J

On behalf of the National Breast Cancer Centre
This *Systematic review of luteinising hormone-releasing hormone agonists in adjuvant therapy of early breast cancer* was prepared by Sharma R, Hamilton A and Beith J on behalf of the National Breast Cancer Centre:

92 Parramatta Road Camperdown, Sydney, Australia
Locked Bag 16 Camperdown NSW 1450
Telephone  +61 2 9036 3030
Facsimile  +61 2 9036 3077
Website  www.nbcc.org.au

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The conclusions of this systematic review are based on evidence available to November 2003. New data are constantly emerging. The conclusions of this systematic review are likely to change with longer follow-up periods and in light of evidence from other trials.

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EXECUTIVE SUMMARY

Luteinising hormone-releasing hormone (LHRH) agonists provide effective ovarian suppression in pre-menopausal women and have been shown to be an acceptable alternative to ovarian ablation by surgery or radiotherapy. In contrast to surgical or radiological methods, LHRH agonists induce a menopausal status that is reversible on cessation of treatment.

The benefits of LHRH agonists in the treatment of pre-menopausal women with hormone receptor-positive advanced breast cancer have been demonstrated. This systematic review was performed to clarify the role of LHRH agonists in the adjuvant treatment of pre-menopausal women with early breast cancer. As ovarian suppression is unlikely to benefit women with oestrogen receptor negative (ER–) tumours, the review is limited to women with oestrogen receptor positive (ER+) disease.

The objectives were to review trials in which LHRH agonists have been:

- integrated into adjuvant hormonal therapy
- integrated into adjuvant chemo-hormonal therapy
- compared with ovarian ablation by surgery or radiotherapy.

Eleven randomised trials were identified. In two trials of pre-menopausal women with early breast cancer, adjuvant suppression of ovarian function using LHRH agonists, with or without TAM, had similar benefits at five to six years follow-up in terms of disease-free survival and overall survival to adjuvant CMF chemotherapy. As the trials reviewed all used control arms that are no longer considered standard, the applicability of these results to current clinical practice is cautioned. However, the findings suggest that ovarian suppression using LHRH agonists is a reasonable alternative to TAM or CMF chemotherapy in women with ER+ tumours who have a contradiction or intolerance to these standard therapies.

The role of chemotherapy in addition to LHRH agonists is not clearly defined and mature results of four trials are awaited. Data are also inadequate at the time of publication to inform decisions about the efficacy of LHRH agonists in comparison with TAM for the treatment of ER+ early breast cancer.
INTRODUCTION

Breast cancer is a major cause of morbidity and mortality in Australian women. Approximately 25% of women diagnosed and treated for breast cancer will eventually die of the disease. The aim of adjuvant therapy is to prevent systemic recurrence and improve overall survival. In pre-menopausal women with early breast cancer, options for adjuvant therapy include cytotoxic chemotherapy, ovarian ablation (with surgery or radiotherapy), ovarian suppression (with LHRH analogues) and anti-oestrogen therapy.

Approximately 60% of breast tumours in pre-menopausal women are hormone receptor-positive and these patients are candidates for hormonal therapy. The goal of hormonal therapy is to inhibit the action of oestrogen. Oestrogen deprivation can be achieved by blocking oestrogen receptors with drugs such as TAM, suppressing oestrogen synthesis with LHRH analogues, or by ovarian ablation either surgically or using radiotherapy.

Chemotherapy induces amenorrhoea in approximately 60% of pre-menopausal women who receive adjuvant treatment. Disease-free survival is better in women with hormone receptor-positive disease who become amenorrhoeic following chemotherapy than in those who do not. This suggests that the efficacy of chemotherapy in pre-menopausal women may in part be endocrine mediated. The benefit of ovarian ablation by either oophorectomy or radiotherapy on overall survival and recurrence-free survival in women with breast cancer has been demonstrated in a meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). This analysis was directed at women under the age of 50 years, most of whom were likely to be pre-menopausal. For women who underwent ovarian ablation in the absence of chemotherapy, there was a 25% reduction in the annual odds of recurrence and a 24% reduction in the annual odds of death compared with no treatment. The benefit was seen in both node-positive and node-negative women. There was a trend for greater benefit of ovarian ablation in women with ER+ tumours, although this was only assessed in a small number of the trials reviewed. In women randomised to ovarian ablation following chemotherapy, the benefit of ablation compared with no treatment was not as pronounced (annual odds of recurrence, 10% and annual odds of death, 8%).

These results were supported by two further trials comparing adjuvant ovarian ablation to CMF chemotherapy. Both trials concluded that, in pre-menopausal women with node-positive disease, both CMF chemotherapy and oophorectomy have similar effects on disease-free survival and overall survival. However, a retrospective subgroup analysis of the Scottish/ICRF trial
suggested that oophorectomy produced a survival benefit in women with ER+ tumours, whereas oral CMF was beneficial for women with ER– tumours.

LHRH agonists provide effective ovarian suppression in pre-menopausal women and are an acceptable alternative to oophorectomy or pelvic radiotherapy. These agents induce a menopausal status that is reversible on cessation of therapy. LHRH agonists act by binding to pituitary LHRH receptors, resulting in down-regulation of these receptors and subsequent suppression of luteinising hormone and oestradiol. The most commonly prescribed LHRH analogue is goserelin. Side effects of LHRH agonists include fertility impairment, decreased libido, hot flushes, sweating, headache, blood pressure changes, loss of bone density, transient increase of pain in bony metastases, hypercalcaemia and a number of other rare complications. A number of clinical trials have shown goserelin to be effective in the treatment of advanced breast cancer in pre-menopausal women with hormone receptor-positive disease, with a response similar to that seen with surgical oophorectomy or ovarian suppression. The role of adjuvant LHRH agonists is now being studied actively in the pre-menopausal setting for women with early breast cancer.

The National Breast Cancer Centre commissioned this systematic review to summarise current evidence about the role of LHRH agonists in the adjuvant treatment of ER+ early breast cancer in pre-menopausal women, with a view to providing evidence to support the information needs of women with breast cancer, clinicians, media and policy makers.
METHODS

Research aim and objectives

The aim of the review was to summarise the literature reporting on trials of LHRH agonists as adjuvant therapy for early breast cancer. Because of the lack of efficacy of hormonal therapy demonstrated in ER– women in these trials, ER– women were excluded from the current systematic review. The specific objectives of the review were to:

- summarise trials in which LHRH agonists have been:
  - integrated into adjuvant hormonal therapy
  - integrated into adjuvant chemo-hormonal therapy
  - compared with ovarian ablation using surgery or radiotherapy
- discuss the impact of amenorrhoea in the long term
- describe the best available evidence pertaining to the optimum duration of LHRH treatment.

Search strategy

An overview of the methods used is presented in Appendix 1. The specialised register maintained by the Secretariat of the Cochrane Breast Cancer Group was searched. Details of the search strategy applied by the Group to create the register, and the procedure used to code references, are described in the Group’s module on the Cochrane Library. The search strategies are detailed in Appendix 2. This was supplemented by hand-searching of reference lists of relevant reviews, presentations by experts in the field and conference proceedings.

At the time of the review, 44 references were found pertaining to randomised trials involving LHRH agonists, and one reference pertaining to a controlled clinical trial involving LHRH agonists.
**Initial selection of trials**

The eligibility criteria for the review were defined prospectively as outlined below.

**Types of trials**

Full articles in peer-reviewed journals and published conference abstracts were considered. In order to be eligible for inclusion, clinical trials had to be randomised and controlled. Only reports published in English were included.

**Types of participants**

Participants were women with early breast cancer (defined as operable breast cancer). No age restrictions were applied. Trials of women with locally advanced or metastatic disease were excluded.

**Types of interventions**

LHRH agonists included buserelin, goserelin, leuprolelin, nafarelin and triptorelin.

**Types of outcome measures**

The primary outcome measure was overall survival. Secondary outcome measures were disease-free survival/recurrence-free survival, quality of life (validated or trial-specific instruments) and toxicity (as defined by National Cancer Institute [NCI], World Health Organisation [WHO] or NCI Canada criteria).
Final selection of trials

Titles of trials identified using the above search strategy were screened for possible eligibility by two reviewers and excluded if clearly ineligible. A copy of the full article or abstract for each reference reporting a potentially eligible trial was obtained. The eligibility criteria were applied to each trial by two independent reviewers. A third reviewer resolved any discrepancies. Reviewers were not blinded to study authors or results during this selection process.

Quality appraisal of trials

Two independent reviewers appraised the design and conduct of each trial to assess its susceptibility to bias. Methodological quality was assessed using a modified subset of the Methods for Evaluating Research and Guideline Evidence (MERGE) criteria. The following aspects of each trial were considered:

- concealment of treatment allocation
- generation of the allocation sequence
- comparability between groups at the baseline
- inclusion of all randomised participants in the analysis
- withdrawals from the trial
- valid assessment of endpoints.

A global quality score was allocated to each trial:

- **Grade A** – all or most evaluation criteria from the checklist are fulfilled. Where evaluation criteria are not fulfilled, the conclusions of the study are thought very unlikely to alter.

- **Grade B1** – some evaluation criteria from the checklist are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought unlikely to alter.
• **Grade B2** – some evaluation criteria from the checklist are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought likely to alter.

• **Grade C** – few or no evaluation criteria are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought very likely to alter.

Where the two reviewers differed in quality assessment, arbitration from a third reviewer was sought.

**Data extraction and analysis**

A single reviewer extracted data describing the trial and patients’ baseline characteristics. Two independent reviewers extracted data on outcomes (including follow-up times, withdrawal rates and crossover rates). A formal meta-analysis of the data was not performed as the trials identified are ongoing and final results have not been reported. A structured abstract was created for each trial identified, accompanied by a commentary to interpret and put into context outcomes from all identified trials. A discussion of the status of future relevant trials and further results follows.
RESULTS

Following application of the eligibility criteria, eleven randomised trials were identified that have addressed the role of LHRH agonists in the adjuvant treatment of pre-menopausal women with ER+ early breast cancer: six were reported only as abstracts and five with full publications. The trials addressed the predefined therapeutic questions as outlined below.

- **Integration into adjuvant hormonal therapy (Table 1):**
  - two trials compared an LHRH agonist with TAM
  - two trials compared an LHRH agonist with combined LHRH agonist and TAM
  - one trial compared TAM with combined LHRH agonist and TAM

- **Integration into adjuvant chemo-hormonal therapy (Table 2):**
  - three trials compared an LHRH agonist with CMF chemotherapy
  - no trials comparing LHRH agonists to other chemotherapeutic regimens were identified
  - one trial compared an LHRH agonist with chemotherapy followed by an LHRH agonist
  - three trials compared combined LHRH agonist and TAM to chemotherapy; only one study used an anthracycline-containing chemotherapy arm
  - four trials compared chemotherapy with chemotherapy followed by an LHRH agonist
  - three trials compared chemotherapy with chemotherapy followed by combined LHRH agonist and TAM

- **Comparison with ovarian ablation by surgery or radiotherapy:**
  - no trials were identified comparing an LHRH agonist to surgical or radiotherapeutic ovarian ablation in the adjuvant setting. A discussion of findings in advanced breast cancer is given on p31.
Structured abstracts of trials

Author & date: Baum M et al. 2001

Trial name: ZIPP

Title of article: Management of pre-menopausal women with early breast cancer: is there a role for goserelin?

TAM vs goserelin vs TAM + goserelin vs no endocrine therapy

Abstract only available (main results). Full publications reporting on side effects.

Design: Multicentre trial; randomised 2 × 2 factorial design.

Patients: 2710 pre-menopausal women with early stage invasive breast cancer.

Treatment: Patients received no adjuvant treatment (n=1356) or goserelin for two years (n=1354). In addition, 1800 patients were also randomised to TAM for two years (control n=899; TAM n=901). ER status did not have to be known. Initial treatment (surgery, radiotherapy, chemotherapy) and whether to randomise to or give TAM electively was predefined by local centres.

Primary outcomes: Recurrence-free survival Side effects of adjuvant endocrine treatment, in particular sexual dysfunction were reported in separate analyses.

Results: Forty three per cent of patients received chemotherapy and 56% were node negative. After a median follow-up of 66 months, women randomised to goserelin had a significantly prolonged recurrence-free survival (relative risk [RR] = 0.8; 95% CI 0.69–0.92; p<0.001). Overall survival was also significantly higher for women receiving goserelin (RR 0.82; 95% CI 0.67–0.99; p=0.04). Subgroup analysis suggests that goserelin had its greatest benefit in patients with ER+ tumours who had not received chemotherapy. However, no tests for heterogeneity were significant. A retrospective subgroup analysis of the effect of goserelin in patients who received TAM was performed. In 860 women randomised to receive TAM, and in 895 women who received TAM electively, the addition of goserelin improved recurrence-free survival compared with TAM alone (RR 0.76 and 0.70, respectively).
Two subgroup analyses comparing side effects and differences in sexuality between the treatment arms were published as full articles. Two hundred and ninety three patients completed questionnaires at seven assessment points. The instrument used was developed by the study centre using the Physical Symptoms and Problem List. The Hospital Anxiety and Depression and Relationship and Sexuality Scale were also used.

Vasomotor symptoms: At 0–24 months there was a significant three-way interaction between chemotherapy, endocrine treatment and time (p=0.05), indicating that chemotherapy had a negative effect on the TAM and no endocrine treatment groups. There was, however, no negative impact on those treated with goserelin and goserelin plus TAM. Likewise, endocrine treatment had no effect on CMF-treated patients but had a differential effect on patients not treated with CMF. In addition, patients treated with goserelin either alone or in combination reported significantly more vasomotor symptoms than the patients treated with TAM alone (p<0.0001). In the analysis based on 0, 30 and 36 months, patients treated with chemotherapy maintained higher adverse symptom levels compared to baseline. In those patients not treated with CMF, vasomotor symptoms decreased after the cessation of endocrine therapy.

Vaginal dryness: At 0–24 months significantly more symptoms related to vaginal dryness were reported by patients who had received chemotherapy than those who had not (p=0.05). Patients receiving goserelin reported more symptoms than any other group. Furthermore, patients receiving TAM alone or in combination with goserelin reported more symptoms than those in the control group. There were no differences between the groups at 36 months. The side effects caused by endocrine therapy decreased with time.

Vaginal discharge: At 0–24 months patients who received TAM alone or in combination reported significantly more vaginal discharge regardless of whether they had received prior chemotherapy. These effects diminished after cessation of treatment.

Changes in body image: At 0–24 months patients receiving CMF reported more problems with changes in body image than those who did not receive CMF. This negative effect of chemotherapy persisted to 30 months but no difference was seen at 36 months. The study suggests that endocrine therapy has adverse effects in patients not treated with CMF. In those not receiving cytotoxic treatment, the negative effects of endocrine treatment were limited to the active treatment period and decreased after cessation of treatment. In contrast, the effects of endocrine therapy in those patients previously treated with chemotherapy persisted at the end of treatment.
Sexuality: This was assessed according to sexual activity, function, frequency and fear. Seventy seven per cent of patients were sexually active. Patients who received chemotherapy reported a higher level of sexual dysfunction than patients who did not receive chemotherapy. The addition of endocrine therapy did not alter this result. Those patients administered chemotherapy maintained a high level of dysfunction throughout the study period and even two to three years later, independent of endocrine treatment. Goserelin alone or in combination with TAM had a negative effect on most parameters of sexuality in those patients who had not previously received chemotherapy from one to two years after inclusion, compared with controls. TAM did not significantly ameliorate the negative effects of goserelin. After cessation of endocrine therapy, sexual dysfunction began to diminish. TAM alone did not produce any side effects and did not differ from control, but it had a positive effect on sexual frequency and intercourse. This may relate to the weak oestrogenic effects on the vaginal epithelium.
CAF₆ vs CAF₆ → goserelin vs CAF₆ → goserelin + TAM

Abstract only available.


Patients: 1504 pre-menopausal women with node-positive, hormone receptor positive early breast cancer.

Treatment: Patients were randomised to:

- CAF (cyclophosphamide 100mg/m² orally q14, doxorubicin 30mg/m² iv d1 and 5-fluorouracil [5FU] 500mg/m² iv d1 and 8) q28d × six cycles
- CAF followed by goserelin (3.6mg sc q28 × five years)
- CAF followed by goserelin and TAM (20mg daily × five years)

Primary outcomes: Disease-free survival and overall survival.

Results: Fifty nine per cent of patients had one to three positive nodes; 29% were < 40 years and 89% were progesterone receptor positive (PR+).

After a median follow-up of 9.6 years, a significant reduction in the hazard ratio (HR) for recurrence was found with the addition of TAM to CAF followed by goserelin (HR 0.73, p<0.01). Addition of goserelin alone following CAF did not improve recurrence (HR 0.93 p=0.25). HRs for overall survival for CAF followed by goserelin + TAM and CAF followed by goserelin alone were 0.91 (p=0.21) and 0.88 (p=0.14), respectively. Retrospective subset analysis suggests that the addition of goserelin to CAF may be beneficial for women <40 years, those who are not
amenorrhoeic after CAF or women who have pre-menopausal oestrodiol levels. Final analyses of the impact of amenorrhoea, patient age and serum hormone levels on clinical outcome are awaited.
Author & date: Jonat W et al. 2002

Title of trial: ZEBRA

Title of article: Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in pre-menopausal patients with node-positive breast cancer: the Zoladex early breast cancer research association study

goserelin vs CMF₆

Full publication available.

Design: International, randomised trial from 102 centres in 15 countries.

Patients: 1614 of 1640 pre- or peri-menopausal women, ≤ 50 years with node-positive, stage II, operable disease enrolled between 1990 and 1996. All women had undergone either mastectomy (n=857) or lumpectomy (n=757) and/or adjuvant radiotherapy (n=1108).

Treatment: Patients were randomised to:

- goserelin (3.6mg depot sc q28d × two years) (n=797)
- CMF (cyclophosphamide 500mg/m² iv d1 and 8, or 100mg/m² orally d1–14, methotrexate 40mg/m² iv d1 and 8, 5FU 600mg/m² iv d1 and 8) q28d × six cycles (n= 817)

Primary outcomes: Disease-free survival and overall survival.

Results: Seventy per cent of patients had one to three positive nodes and 25% had four to nine positive nodes. ER status was known for 92.5% of patients; 80% of patients were ER+.

After a median follow-up of six years, 357 patients (44.8%) randomised to goserelin and 327 (40%) randomised to CMF had an event. HR for disease-free survival was 1.18 (95% CI 1.02–1.37; p=0.029). In patients with ER+ tumours, goserelin was equivalent to CMF for disease-free survival (HR 1.01; 95% CI 0.84–1.2; p=0.94) and overall survival (HR 0.99; 95% CI 0.76 to 1.28; p=0.92).

Ninety five per cent of patients treated with goserelin and 58.6% of patients treated with CMF became amenorrhoeic after six months of treatment. After three years, only 22.6% of patients who
had received goserelin remained amenorrhoeic compared with 76.9% of patients treated with CMF. The incidence of menopausal side effects, hot flushes, vaginal discharge and vaginal soreness, were similar in both groups. These side effects resolved after ceasing goserelin but persisted in the CMF arm. No grade 3 or 4 symptoms were reported.

Bone mineral density (BMD) of the lumbar spine (L2–L4) and neck of femur was assessed in 96 patients from eight centres. At two years, the mean percentage BMD loss at the lumbar spine in women receiving goserelin was −10.5% compared with −6.5% for women receiving CMF (p=0.0005). BMD loss at the neck of femur was −6.4% and −4.5% in women receiving goserelin and CMF, respectively (p=0.04). At three years, mean percentage BMD loss for goserelin and CMF at the lumbar spine was −6.2% and −7.2%, respectively (p=0.26) and at the neck of femur was −3.1% and −4.6%, respectively (p=0.48).

Quality of life assessment was performed by 86 centres using the Rotterdam Symptom Checklist supplemented by additional questions. An initial improvement in quality of life from baseline was seen in women receiving goserelin but no difference was seen after six months of treatment.
**Author & date:** Castiglione-Gertsch M *et al.* 2002

**Title of trial:** IBCSG 8

**Title of article:** Is the addition of adjuvant chemotherapy always necessary in node negative (N–) pre/peri-menopausal breast cancer patients (pts) who receive goserelin?: first results of IBCSG trial VIII

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goserelin vs CMF<sub>6</sub> vs CMF<sub>6</sub> → goserelin vs no adjuvant treatment

Abstract only available.

**Design:** Randomised trial.

**Patients:** 1063 women with node-negative breast cancer who had received either mastectomy (45%) or breast-conserving therapy with axillary clearance of at least eight nodes.

**Treatment:** Women were randomised to:

- goserelin alone (3.6mg sc monthly for 24 months)
- CMF × six cycles
- CMF × six cycles followed by goserelin for 18 months
- no adjuvant treatment.

**Primary outcomes:** Disease-free survival and overall survival.

**Results:** Receptor status was known in 97% of patients; 70% of patients had ER+ tumours; 19% were < 39 years; and 62% had tumours < 2cm. The ‘no treatment’ arm was discontinued with 46 patients enrolled. After a median follow-up of 5.7 years, five-year disease-free survival was 61% in patients receiving no treatment, 79% in patients randomised to goserelin alone, 82% in patients receiving CMF alone and 88% in patients receiving sequential therapy. In patients with ER+ tumours, five-year overall survival was similar for all three treatment groups (81%, 81% and 88%, respectively).
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CMF₆ vs leuprolerin

Full publication available. Interim analysis.

**Design:** Randomised trial conducted in 71 centres in Germany and the Ukraine.

**Patients:** 589 pre- or peri-menopausal women with ER+ or unknown hormonal status, stage II or IIIA breast cancer with axillary node involvement were enrolled between 1995 and 1999. Interim analysis available for 227 patients. Eligibility criteria were amended in March 1998 to include only women with ER+ disease.

**Treatment:** All women underwent either mastectomy (n=130) or lumpectomy (n=109) and/or adjuvant radiotherapy (n=9). Patients were randomised to:

- CMF (cyclophosphamide 100mg/m² orally d1–14, methotrexate 40mg/m² iv d1 and 8, and 5FU 600mg/m² iv d1 and 8) q28d × six cycles (n=117)
  - leuprolerin acetate 11.5mg every 3 months for 2 years (n=110).

**Primary outcomes:** Recurrence-free survival.

**Results:** One hundred and sixty one patients had one to three positive nodes and 63 patients had more than four positive nodes. After a median follow-up of 24 months in the leuprolerin group and 22 months in the CMF group, mean progression-free survival was 750 days (95% CI 694–806) in the leuprolerin group and 771 days (95% CI 717–824) in the CMF group (p=0.94). Two-year recurrence-free survival was 59.1% for patients treated with leuprolerin and 45.3% for those treated with CMF.
All women treated with leuprolrelin became amenorrheic during the treatment period. One hundred and three patients (90.4%) treated with CMF became amenorrheic. The onset of amenorrhea was earlier in those treated with leuprolrelin. Suppression of menstruation lasted the entire observation period in 80.9% and 61.2% of patients treated with leuprolrelin and CMF, respectively.

The most frequently reported side effects in the leuprolrelin arm were hot flushes (80.9%), weight gain (79.1%) and increased sweating (77.3%). In patients treated with CMF the most common reported side effects were alopecia (62.4%), nausea (86.3%) and vomiting (55.6%). Hot flushes and weight gain were more common in leuprolrelin arm. Grade 3 side effects occurred in 11.1% of patients treated with CMF and 8.4% of those treated with leuprolrelin. The nature of these side effects was not reported.

Overall self-assessment of tolerability by patients was markedly better after three and six months of treatment in the leuprolrelin group compared with the CMF group. No difference in self-assessment of tolerability was noted after two years.
CMF$_6$ vs TAM + ovarian ablation/suppression

Full publication available.

**Design:** Randomised Italian trial carried out in 17 centres.

**Patients:** 244 pre- or peri-menopausal women with operable disease entered on trial between 1989 and 1997. Patients were aged 35–55 years with either node-positive or poorly differentiated ER+ tumours.

**Treatment:** All women underwent either mastectomy (n=130) or lumpectomy (n=109) and/or adjuvant radiotherapy (n=9). Patients were randomised to:

- CMF (cyclophosphamide 100mg/m$^2$ orally d1–14, methotrexate 40mg/m$^2$ iv d1 and 8, and 5FU 600mg/m$^2$ iv d1 and 8) q28d × six cycles (n=120)

- TAM (30mg/d × 5 years) combined with ovarian ablation/suppression (n=124). Ovarian ablation/suppression consisted of either surgical oophorectomy, ovarian irradiation through a 15cm × 15cm pelvic port for a total dose of 15Gy or medical castration using goserelin (3.6mg depot sc q28d × two years).

**Primary outcomes:** Disease-free survival and overall survival.

**Results:** One hundred and fifty patients had one to three positive nodes and 59 patients had more than four positive nodes. After a median follow-up of 76 months, the relative risk of recurrence for
CMF compared with TAM + ovarian ablation/suppression was 0.94 (95% CI 0.6–1.47; p=0.8), and the relative risk of recurrence and/or death was 0.69 (95% CI 0.36–1.33; p=0.3).

All women treated with goserelin (n=70) became amenorrhoeic during the treatment period. Fourteen of these patients (20%) recommenced menstruation after discontinuation of treatment. Of the 106 women treated with CMF, 72 (68%) of women became amenorrhoeic during treatment and remained so after cessation of treatment. Menopausal symptoms were more prevalent in the TAM + ovarian ablation/suppression arm than the CMF arm.
goserelin + TAM vs CMF

Full publication available.

Design: Multicentre Austrian trial conducted between 1990 and 1999.

Patients: 1034 of 1099 pre-menopausal women, with ER+, stage I or II disease who had undergone either mastectomy or lumpectomy and/or adjuvant radiotherapy.

Treatment: Patients were randomised to:

- goserelin (3.6mg depot sc q28d × three years) and TAM (20mg daily × five years) (n=511)
- CMF (cyclophosphamide 600mg/m² iv d1 and 8, methotrexate 40mg/m² iv d1 and 8, and 5FU 600mg/m² iv d1 and 8) q28d × six cycles (n=523).

Primary outcomes: Recurrence-free survival and overall survival.

Results: Ninety three per cent of patients had ER+ tumours and 90% had PR+ tumours.

After a median follow-up of 60 months, 41 (8%) patients had died in the endocrine arm compared with 51 (10%) patients in the CMF chemotherapy arm. Local recurrence occurred in 24 (5%) patients in the endocrine arm and 42 (8%) patients in the chemotherapy arm. At five years, disease-free survival for the endocrine arm was 81% compared with 76% for the chemotherapy arm (p=0.037). Survival data are not yet mature. There is a suggestion of a non-significant improvement in HR in favour of treatment with TAM + goserelin (p=0.195). Flushing was more prevalent in the endocrine arm than in the chemotherapy arm (91% vs 54%).
Author & date: Roche H et al. 2000

Title of trial: FASG06 (French study)

Title of article: Complete hormonal blockade versus chemotherapy in pre-menopausal early-stage breast cancer patients (pts) with positive hormone-receptor (HR+) and 1–3 node-positive (N+) tumor: results of the FASG 06 trial

triptorelin + TAM vs FEC₆

Abstract only available.


Patients: 333 pre-menopausal women with ER+, node-positive (1–3 lymph nodes involved), operable breast cancer.

Treatment: Patients were randomised to:

- triptorelin (3.75mg im every month) and TAM (30mg daily) × three years (n=164)
- FEC₅₀ (epirubicin 50mg/m² iv d1 and 8, cyclophosphamide 500mg/m², and 5FU 500mg/m² iv d1 and 8) q21d × six cycles (n=169).

Primary outcomes: Disease-free survival and overall survival.

Results: After a median follow-up of 54 months, there were 22 (13.5%) and 32 (19%) relapses in the endocrine arm and chemotherapy arm, respectively, with a disease-free survival of 91.7% and 80.9% (p=0.12). Seven (4.3%) patients died in the LHRH agonist arm compared with 13 (7.7%) patients in the chemotherapy arm, with an overall survival rate of 97% and 92.9%, respectively (p=0.18). Amenorrhoea was induced by chemotherapy in 68 (41.5%) patients.
Author & date: Soreide JA et al. 2002

Title of trial: Norwegian study

Title of article: Adjuvant endocrine treatment (goserelin vs. TAM) in pre-menopausal patients with operable node positive stage II breast cancer: A prospective randomised national multicenter study

TAM vs goserelin

Full publication available.

Design: Norwegian multicentre, prospective, randomised trial.

Patients: 320 pre-menopausal patients with node-positive, operable, stage II breast cancer enrolled between 1989 and 1994. Women with ER+ and unknown receptor status (n=76) were included in the study but ER– patients were excluded. 255 women underwent mastectomy and 140 patients received adjuvant radiotherapy.

Treatment: Patients were randomised to:

- TAM (20mg daily) (n=161)
- goserelin (3.6mg depot sc q28d × 2 years) (n=159).

All patients under the age of 70 years were offered adjuvant chemotherapy with vincristine, cyclophosphamide, and 5FU. Methotrexate was substituted for 5FU on day seven.

Primary outcomes: Time to disease recurrence and overall survival.

Results: Two hundred and thirty patients had three or fewer lymph nodes involved. After a median follow-up of 88 months, there was no difference in time to first recurrence (median 87 months) or overall survival between the two treatment arms. The relative risk of recurrence with goserelin compared with TAM was 1.10 (95% CI 0.81–1.49; p=0.56) and the relative risk of death was 1.16 (95% CI 0.80–1.69; p=0.42).
Author & date: Bianco AR et al. 2001

Title of trial: MAM-1 GOCSI

Title of article: The MAM-1 GOCSI trial: a randomised trial with factorial design of chemo-endocrine adjuvant treatment in node positive (N+) early breast cancer (ebc)

CMF vs CMF -> goserelin + TAM vs doxorubicin -> CMF vs doxorubicin -> CMF -> goserelin + TAM

Abstract only available.

Design: Multicentre Italian trial; randomised 2 x 2 factorial design.

Patients: 466 pre-menopausal women with node-positive disease.

Treatment: Patients were randomised to:

- CMF

- doxorubicin followed by CMF

- CMF followed by goserelin and TAM for two years

- doxorubicin followed by CMF followed by goserelin plus TAM for two years.

The study compared 1 and 3 versus 2 and 4 and 1 and 2 versus 3 and 4.

Primary outcomes: Disease-free survival and overall survival.

Results: After median follow-up of five years there was no significant difference in the rate of relapse between anthracycline-containing arms and arms not containing anthracycline (HR 0.86; p=0.42). The addition of combined endocrine therapy significantly reduced the risk of relapse (HR 0.71; p=0.04) compared with chemotherapy alone. Corresponding HRs for overall survival were 0.79 for anthracycline compared with non-anthracycline arms (p=0.31) and 0.86 for combined endocrine therapy compared with chemotherapy alone (p=0.52).
Author & date: Falkson CI et al. 2001

Title of trial: U Pretoria

Title of article: Cyclophosphamide, methotrexate and fluorouracil (CMF) plus or minus depo-buserelin in pre-menopausal women with lymph node positive breast cancer

CMF vs CMF → buserelin

Abstract only available.

Design: Prospective, randomised trial.

Patients: 145 of 150 pre-menopausal women with node-positive disease.

Treatment: Patients were randomised to CMF (n=75) or CMF and depo-buserelin (n=72) for an unspecified time duration.

Primary outcomes: Disease-free interval (DFI) and overall survival.

Results: Median DFI for patients receiving CMF alone was 6.2 years compared with 6.8 years for patients receiving combined treatment. The difference was not statistically significant. Median survival in the combined treatment group was 10.9 years. Survival data for CMF alone arm was not mature. More hot flushes were reported in the combination arm but other toxicities were similar.
DISCUSSION

Trials addressing integration of LHRH agonists into adjuvant hormonal therapy

LHRH agonist compared with TAM

The Norwegian study did not demonstrate a statistical difference in time to recurrence or overall survival between goserelin and TAM, but the study has limited statistical power (n=320).22

The ZIPP trial2 used treatment arms of goserelin alone and TAM alone, each with approximately 450 patients. However, no comparison of goserelin with TAM has yet been reported. It should be noted that the randomisation was performed in a 2 × 2 factorial fashion (goserelin vs no goserelin, TAM vs no TAM) and results from comparisons of individual arms may not be presented in any detail in future reports.

Conclusion: Data are currently inadequate to inform conclusions about the relative efficacy of LHRH agonists compared with TAM.

LHRH agonist compared with combined LHRH agonist + TAM

The INT 0101 trial has arms in which women received CAF chemotherapy followed by goserelin (CAF-Z) or CAF followed by goserelin and TAM (CAF-ZT).6 The three-way randomisation and statistical design allows comparison of CAF-Z with CAF-ZT. A significant disease-free survival benefit of CAF-ZT was found compared with CAF-Z at a median follow-up of 9.6 years (p<0.01). However, no significant difference was seen in overall survival between the two arms.

As discussed above, the ZIPP trial2 contained treatment arms of goserelin alone and goserelin in combination with TAM but the most recent report does not compare LHRH with LHRH + TAM, and as explained above, this comparison may not be available from future reports.
Conclusion: No conclusive benefit of the addition of TAM to an LHRH agonist has been demonstrated.

**TAM vs combined LHRH agonist + TAM**

The ZIPP trial contained treatment arms of TAM alone or in combination with goserelin. Patients may have received TAM electively or by a second randomisation. Retrospective analysis suggests that the addition of goserelin to TAM significantly improved EFS compared with TAM alone (RR 0.76 and 0.70, respectively). It should be noted that this subgroup analysis does not control for ER status (33% of the overall population in this study were ER–, and another 23% were of unknown ER status), or the use of chemotherapy (43% of patients received chemotherapy). Overall survival has not been reported.

Conclusion: No conclusive benefit from the addition of an LHRH agonist to TAM has been demonstrated.

**Trials addressing integration of LHRH agonists into adjuvant chemo-hormonal therapy**

**LHRH agonist vs CMF chemotherapy**

The ZEBRA trial randomised 1614 women, 1189 of whom had ER+ disease, to goserelin or CMF. The study showed that at six-year follow-up, CMF was superior to goserelin in terms of disease-free survival, but no difference was detected in overall survival. In women with ER+ disease, no difference in disease-free survival or overall survival was detected between women who received CMF or goserelin.

IBCSG 8 was initially designed as a 2 × 2 factorial design of CMF and goserelin, but the observation arm was dropped after 46 patients were enrolled. In 475 patients with ER+ disease, no difference in five-year disease-free survival was seen between patients receiving goserelin or CMF (81% vs 81%).
The TABLE study\textsuperscript{19} randomised 589 women with ER+ disease to leuprorelin or CMF. In the published interim analysis at 2 years, 227 women were eligible for assessment, 210 of whom were ER+. The analysis showed no difference in progression free survival between the two treatment arms.

**Conclusion:** LHRH agonists are equivalent in efficacy to CMF chemotherapy at two to six years of follow-up.

**LHRH agonist vs CMF followed by LHRH agonist**

IBCSG 8\textsuperscript{5} randomised 472 women between goserelin and CMF followed by goserelin. No difference in five-year disease-free survival was detected between the two arms (81\% vs 88\%, respectively; RR 0.86; p=0.46).

**Conclusion:** No benefit from the addition of CMF to a LHRH agonist has been demonstrated.

**LHRH agonist + TAM vs chemotherapy**

The Austrian study\textsuperscript{21} randomised 1099 women, 93\% of whom were ER+ to goserelin + TAM, or CMF. At a median follow-up of five years, there was a significant advantage to goserelin and TAM over CMF in disease-free survival (81\% vs 76\%, p=0.037). There was a non-significant advantage to goserelin and TAM in overall survival.

The Italian study\textsuperscript{20} also compared goserelin + TAM with CMF. No difference in disease-free survival or overall survival was demonstrated in this study (n=244).

The French study\textsuperscript{18} is the only randomised comparison of a LHRH agonist-based hormonal therapy and an anthracycline-based chemotherapy. No differences in disease-free survival or overall survival were demonstrated between women receiving triptorelin + TAM or FEC\textsubscript{50} (n=333). The epirubicin dose used in this study (50mg/m\textsuperscript{2}) has since been shown to be inferior to an alternative schedule of the same drug (100mg/m\textsuperscript{2} dose).\textsuperscript{28}

**Conclusion:** Combined hormonal therapy is equivalent in efficacy to non-anthracycline chemotherapy and sub-optimal anthracycline chemotherapy.
CMF/CAF chemotherapy vs CMF/CAF chemotherapy followed by LHRH agonist

IBCSG 8\(^8\) randomised 489 women between CMF and CMF followed by goserelin. No difference was detected in five-year disease-free survival between the two arms (81\% vs 88\%, respectively; RR 0.73; p=0.16).

INT 0101\(^6\) randomised approximately 1000 women between CAF and CAF plus goserelin. No significant difference was demonstrated in either disease-free survival or overall survival between the two arms.

In the ZIPP trial,\(^2\) 356 women with ER+ disease received adjuvant chemotherapy before randomisation between goserelin and no goserelin. No significant difference was demonstrated in either disease-free survival or overall survival between the two arms in this subgroup.

**Conclusion:** No benefit from the addition of a LHRH agonist to adjuvant CMF or CAF chemotherapy has been demonstrated.

CMF/doxorubicin chemotherapy vs CMF/doxorubicin chemotherapy followed by LHRH agonist + TAM

In MAM-1,\(^7\) 466 women were randomised to receive either chemotherapy (CMF or doxorubicin followed by CMF, in a separate randomisation), or chemotherapy plus goserelin and TAM. The addition of combined hormonal therapy significantly reduced the risk of relapse (HR 0.71; p=0.04), but no difference in overall survival was demonstrated.

U Pretoria\(^23\) compared CMF with CMF followed by buserelin (n=145). No differences in outcome were observed.

In the ZIPP trial,\(^2\) 3\% of patients received adjuvant chemotherapy prior to randomisation between hormonal therapies, in a 2×2 design. A subgroup of patients randomly received either goserelin and TAM or no further therapy following chemotherapy, but results for this comparison have not been reported, and are unlikely to be highlighted in future publications.
**Conclusion:** No conclusive benefit from the addition of a LHRH agonist and TAM to adjuvant chemotherapy with CMF or doxorubicin has been demonstrated.

**Trials comparing LHRH agonists with ovarian ablation by surgery or radiotherapy**

No trials were identified that compared LHRH agonist-induced ovarian suppression with ovarian ablation by surgery or radiotherapy. Extrapolating from the trials performed in advanced breast cancer, it could be hypothesised that both surgical ablation of the ovaries and ovarian suppression using LHRH agonists would have similar benefits in terms of disease-free survival and overall survival. The complications of early menopause, including accelerated bone loss, vascular disease and infertility, are likely to be influenced by the age distribution of the women receiving treatment: younger women will experience a longer duration of additional menopause than women closer to the age of natural menopause. As surgical ablation is permanent, compared with the reversible ovarian suppression seen with LHRH agonists, women undergoing surgical ablation are more likely to experience these complications.

**Long-term effects of amenorrhoea**

A reduction in BMD, as described earlier, is the only long-term effect of amenorrhoea secondary to LHRH agonists reported in these trials. The ZEBRA study\(^4\) reported a significant loss of BMD at the lumbar spine and neck of femur in patients treated with goserelin for two years. At three years, BMD had improved at both sites.

Data comparing the long-term effects of amenorrhoea induced by LHRH agonists with surgical or radiological ovarian ablation are limited at the time of publication.

**Duration of LHRH agonist treatment**

There are no trials specifically comparing different durations of LHRH agonist treatment. The trials discussed in this review each used LHRH agonists for varying time periods, most commonly two to three years (Table 3). In INT 0101 patients were treated with goserelin for five years\(^6\) and this was well tolerated by patients. There is a need, however, for further trials addressing treatment duration.
Toxicity/quality of life trials

Detailed information regarding toxicity is addressed by a sub-study of the ZIPP trial. Patients were required to complete questionnaires at seven assessment points during the study: after surgery and before randomisation, and at three to four months, 12 months, 18 months, 24 months, 30 months and 36 months after randomisation. The results suggest that endocrine therapy had differential effects only in patients not treated with CMF. In patients who only received endocrine therapy, menopausal symptoms were confined to the treatment period and decreased during follow-up, whereas in patients previously treated with CMF the side-effects persisted. This may be explained by chemotherapy-induced ovarian ablation.

Patients receiving goserelin alone or in combination with TAM reported a higher degree of vasomotor symptoms than those receiving TAM alone. Patients treated with CMF reported significantly more changes with body image (p=0.001) and a higher degree of sexual dysfunction than those not receiving CMF, with sexual dysfunction persisting even at three years after randomisation. In contrast, goserelin, either alone or in combination, resulted in a higher level of dysfunction in two years of treatment compared to no treatment but this improved after cessation of treatment.

The Austrian trial recorded a higher percent of patients experiencing menopausal-type symptoms with goserelin and TAM compared with CMF, and more nausea and alopecia with CMF. This is representative of all the reported trials, as LHRH agonists result in a more abrupt menopausal state compared with cytotoxic chemotherapy. It is noted that menopausal symptoms improved after cessation of endocrine therapy but persisted in those receiving cytotoxic chemotherapy.

The ZEBRA study used the Rotterdam Symptom Checklist to assess quality of life. Questionnaires were completed at baseline and at least one post-baseline measure was taken. In the first three to six months, patients randomised to goserelin had significantly better scores for physical symptoms, activity level and ability to cope with illness compared to patients receiving CMF (p<0.00001). After six months there was no significant difference between the two groups. The positive change from baseline in overall quality of life score was significantly greater in the goserelin group during the first three to six months (p<0.00001), while at one, two and three years there was no difference.
Cost of drugs

The cost of full courses of each of the endocrine arms for each trial has been calculated. Where the treatment regimen for goserelin was not listed (in three of nine trials) it was assumed to be 3.6mg every 28 days for two years. The dose of TAM was assumed to be 20mg daily unless specified. The Pharmaceutical Benefits Scheme (PBS)-listed price was used to calculate the costs. Only the costs of endocrine agents were considered. Administration, nursing, hospital and pharmacy costs, and costs of management of toxicities were not considered.

The estimated costs for each regimen are shown in Table 4.

Current availability and utilisation of LHRH agonists

In Australia, the Therapeutic Goods Administration (TGA) regulates the registration of drugs and indications, while the Pharmaceutical Benefits Advisory Committee (PBAC) advises the federal government whether to subsidise the use of drugs. At the time of publication, use of goserelin (Zoladex®) is authorised and subsidised for ‘treatment of pre-menopausal women with hormone-dependent advanced breast cancer’. Goserelin is the only LHRH agonist approved for the treatment of breast cancer in Australia.

Future research

There are a number of relevant questions that still remain unanswered. Firstly, the duration of therapy with LHRH agonists needs to be addressed. Secondly, whether women who retain menses despite chemotherapy benefit from LHRH agonists, as suggested by INT 0101, is being addressed by IBSCG Suppression of Ovarian Trial (SOFT) (Table 5). The PERCHE trial (Premenopausal Endocrine-Responsive Chemotherapy Trial) will address the concept of whether chemotherapy adds to optimal adjuvant endocrine therapy in premenopausal women. Further clarification is also required with regards to LHRH agonists versus TAM. Finally, the role of aromatase inhibitors in the treatment of adjuvant breast cancer needs further investigation, particularly in those women made post-menopausal by either chemotherapy or ovarian suppression/ablation (TAM/exemestane trial). These issues are being addressed by a number of trials and results are awaited (Table 5).
Clinical interpretation of findings

In pre-menopausal women with ER+ disease who are not candidates for chemotherapy:

- TAM remains the endocrine treatment of choice
- LHRH agonists are an acceptable alternative in women with a contraindication or intolerance to TAM
- combined hormonal therapy has no demonstrated benefit over single-agent therapy in the adjuvant setting.

In pre-menopausal women with ER+ disease who are candidates for chemotherapy:

- anthracycline-based chemotherapy followed by TAM remains the standard of care
- LHRH agonists are an acceptable alternative to non-anthracycline chemotherapy in women with a contraindication or intolerance to anthracycline therapy.

Definitive recommendations based on the outcomes of these trials are cautioned. All trials used control arms that are no longer considered standard and individual trial numbers are small.
CONCLUSIONS

Endocrine therapies are ineffective in pre-menopausal women who have ER- tumours. Findings from this review are therefore applicable only to those women with ER+ tumours. This review indicates that LHRH agonists are well tolerated and have a different side-effect profile to that of TAM or chemotherapy. Whilst there are no trials comparing LHRH agonists with ovarian ablation via radiotherapy or surgery, they appear to be an effective alternative for women with early breast cancer.

One major limitation of the trials reviewed is that they all used control arms that are no longer considered standard and therefore the applicability of these results to current clinical practice is cautioned. Individual trial numbers are small and a meta-analysis of the data once trials have matured may be helpful in delineating further the role of LHRH agonists although variability in both entry criteria of each trial and the treatment given may make this difficult.
APPENDICES

Appendix 1  Flow chart of review methodology

1. Search of Cochrane Breast Group specialised register

2. Supplemented by hand-searching of reference lists of relevant reviews, presentations by experts in the field, and conference proceedings

3. Titles screened by two reviewers and excluded if clearly ineligible

4. Abstracts obtained for potentially eligible trials, and assessed independently by two reviewers for eligibility

5. Full publication obtained for potentially eligible trials, and assessed independently by two reviewers for eligibility

6. Single reviewer extracted data describing the study, patient demographics, and toxicities

7. Two reviewers extracted outcomes data

8. Structured abstracts were prepared for each trial by a single reviewer and checked for content by a second reviewer. Discussion and commentary finalised by three reviewers.
Appendix 2  Search strategies

The following searches of the Cochrane Breast Cancer Group specialised register were conducted:

All Non-Indexed Text Fields containing: {goserelin acetate} OR {goserelin} OR {zoladex} OR {leuprolide} OR {lucrin} OR {leuprolin acetate} OR {luteinising hormone-releasing hormone agonists} OR {triptorelin} OR {buserelin} OR {nafarelin} OR {triptorelin}

NOT keywords advanced
### Appendix 3  Tables of results (list of abbreviations in Appendix 4)

Table 1  Trials addressing integration of LHRH agonists into adjuvant hormonal therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>N evaluable</th>
<th>Design</th>
<th>Median follow-up</th>
<th>Population</th>
<th>Publication</th>
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| Soreide JA et al. 2002; Norwegian study | 320         | 1) (± chemo) → G  
2) (± chemo) → TAM | 87 months | Pre-menopausal N+, operable stage II breast cancer | Full publication | B1     |
| Baum M et al. 2001; ZIPP | 2710 | 1) (± chemo) → nil  
2) (± chemo) → G  
3) (± chemo) → TAM  
4) (± chemo) → G + TAM | Not reported | Pre-menopausal Early stage invasive breast cancer | Abstract    |        |
| **LHRH vs LHRH + TAM**|             |                      |                  |                                     |              |        |
| Baum M et al. 2001; ZIPP | 2710 | 1) (± chemo) → nil  
2) (± chemo) → G  
3) (± chemo) → TAM  
4) (± chemo) → G + TAM | Not reported | Pre-menopausal Early stage invasive breast cancer | Abstract    |        |
| Davidson N et al. 2003; E5188 / INT 0101 | 1504 | 1) CAF  
2) CAF → G  
3) CAF → G + TAM | 9.6 yr | Pre-menopausal N+, HormR+ early breast cancer | Abstract    |        |
| **TAM vs LHRH + TAM**|             |                      |                  |                                     |              |        |
| Baum M et al. 2001; ZIPP | 2710 | 1) (± chemo) → nil  
2) (± chemo) → G  
3) (± chemo) → TAM  
4) (± chemo) → G + TAM | Not reported | Pre-menopausal Early stage invasive breast cancer | Abstract    |        |

*Full publications only

42 Systematic review of luteinising hormone-releasing hormone agonists in the adjuvant therapy of early breast cancer
Table 2  Trials addressing integration of LHRH agonists into chemo-hormonal therapy

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<td>Castiglione-Gertsch M et al. 2002(^{15}); IBCSG 8</td>
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<td>N− breast cancer</td>
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<td>Schmid P et al. 2002(^{19}); TABLE</td>
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<td>1) Ov Supp + T</td>
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<td>Jakesz R et al. 2002(^{21}); Austrian Breast and Colorectal Cancer Study</td>
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\(^{*}\)Full publications only
Table 2  Trials addressing integration of LHRH agonists into chemo-hormonal therapy (cont’d)

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<td>Falkson CI <em>et al.</em> 2001; U Pretoria</td>
<td>145</td>
<td>1) CMF</td>
<td>Not reported</td>
<td>Pre-menopausal N+ breast cancer</td>
<td>Abstract</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) CMF→B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemo vs Chemo → LHRH + TAM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davidson N <em>et al.</em> 2003; E5188</td>
<td>1504</td>
<td>1) CAF</td>
<td>9.6 yr</td>
<td>Pre-menopausal N+, HormR+ early breast cancer</td>
<td>Abstract</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) CAF→G</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) CAF→G + T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2  Trials addressing integration of LHRH agonists into chemo-hormonal therapy (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>N evaluable</th>
<th>Design</th>
<th>Median follow-up</th>
<th>Population</th>
<th>Publication</th>
<th>Grade*</th>
</tr>
</thead>
</table>
| Bianco AR *et al.* 2001; MAM-1 GOCSI | 466         | 1) CMF or A → CMF  
2) CMF → G + T or A → CMF → G + T | 5 yr             | Pre-menopausal N+ breast cancer               | Abstract    |        |
| Baum M *et al.* 2001; ZIPP | 2710        | 1) (± chemo) → nil  
2) (± chemo) → G  
3) (± chemo) → T  
4) (± chemo) → G + T | Not reported     | Pre-menopausal Early stage invasive breast cancer | Abstract    |        |

*Full publications only*
Table 3  Type of LHRH agonist used and duration of use in each study

<table>
<thead>
<tr>
<th>Study name</th>
<th>LHRH agonist and dose</th>
<th>Duration of treatment</th>
<th>Tamoxifen population</th>
<th>Tamoxifen dose &amp; duration</th>
<th>ER+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZIPP2</td>
<td>Goserelin</td>
<td>2 yrs</td>
<td>n = 201</td>
<td>dose unknown; 2 yrs</td>
<td>unknown</td>
</tr>
<tr>
<td>E5188 / INT 01016</td>
<td>Goserelin 3.6mg sc q28d</td>
<td>5 yrs</td>
<td>unknown</td>
<td>20mg/day; 5 yrs</td>
<td>unknown</td>
</tr>
<tr>
<td>ZEBRA4</td>
<td>Goserelin 3.6mg sc q28d</td>
<td>2 yrs</td>
<td>–</td>
<td>–</td>
<td>80% (of 92.5% known)</td>
</tr>
<tr>
<td>IBCSG 85</td>
<td>Goserelin 3.6mg sc q28d</td>
<td>2 yrs or 18 mo</td>
<td>–</td>
<td>–</td>
<td>70% (of 97% known)</td>
</tr>
<tr>
<td>TABLE study19</td>
<td>Leuprolelin 11mg q3mo</td>
<td>2 yrs</td>
<td>–</td>
<td>–</td>
<td>all ER+ or receptor status unknown</td>
</tr>
<tr>
<td>Italian Breast Cancer Adjuvant Study20</td>
<td>Goserelin 3.6mg sc q28d</td>
<td>2 yrs</td>
<td>n = 124</td>
<td>30mg/day; 5 yrs</td>
<td>unknown</td>
</tr>
<tr>
<td>Austrian Breast and Colorectal Cancer Study21</td>
<td>Goserelin 3.6mgsc q28d</td>
<td>3 yrs</td>
<td>n = 511</td>
<td>20mg/day; 5 yrs</td>
<td>93%</td>
</tr>
<tr>
<td>FASG06 (French study)18</td>
<td>Triptorelin 3.75mg im q28d</td>
<td>3 yrs</td>
<td>n = 164</td>
<td>30mg/day; 3 yrs</td>
<td>100%</td>
</tr>
<tr>
<td>Norwegian study22</td>
<td>Goserelin 3.6mg sc q28d</td>
<td>2 yrs</td>
<td>n = 161</td>
<td>20mg/day</td>
<td>all ER+ or receptor status unknown</td>
</tr>
<tr>
<td>MAM-I GOCSI7</td>
<td>Goserelin; dose unknown</td>
<td>2 yrs</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>U Pretoria23</td>
<td>Buserelin; dose unknown</td>
<td>unknown</td>
<td>–</td>
<td>–</td>
<td>unknown</td>
</tr>
</tbody>
</table>
Table 4  Study outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>N evaluable</th>
<th>Expt</th>
<th>Median follow-up</th>
<th>Comparator</th>
<th>Outcome measures</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZIPP²</td>
<td>2710</td>
<td>G</td>
<td>66 months</td>
<td>No adjuvant treatment</td>
<td>RR OS</td>
<td>0.82 (p=0.04)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR RFS</td>
<td>0.8 (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>E5188 / INT 0101⁶</td>
<td>1504</td>
<td>CAF</td>
<td>9.6 yr</td>
<td>CAF → G or CAF → G + TAM</td>
<td>HR RFS</td>
<td>0.73 (p&lt;0.01) (CAF v CAF → G + TAM)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR OS</td>
<td>0.93 (p=0.25) (CAF v CAF → G)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91 (p =0.21) (CAF v CAF → G + TAM)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.88 (p=0.14) (CAF v CAF → G)</td>
<td></td>
</tr>
<tr>
<td>ZEBRA⁴</td>
<td>1614</td>
<td>G</td>
<td>6 yr</td>
<td>CMF</td>
<td>HR DFS</td>
<td>1.01 (p=0.94) (ER+ patients)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR OS</td>
<td>0.99 (p=0.92) (ER+ patients)</td>
<td></td>
</tr>
<tr>
<td>IBCSG 8³</td>
<td>1063</td>
<td>G</td>
<td>5.7 yr</td>
<td>CMF or CMF → G</td>
<td>5-yr DFS</td>
<td>79% (G); 92% (CMF); 88% (CMF → G)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5yr OS</td>
<td>81% (G); 81% (CMF); 88% (CMF → G)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(ER+ only for 5yr OS)</td>
<td></td>
</tr>
<tr>
<td>TABLE study¹⁹</td>
<td>227</td>
<td>L</td>
<td>22–24 months</td>
<td>CMF</td>
<td>2yr RFS</td>
<td>45.3% (CMF); 59.1% (L)</td>
<td></td>
</tr>
<tr>
<td>Italian Breast Cancer Adjuvant Study²⁰</td>
<td>244</td>
<td>CMF</td>
<td>76 months</td>
<td>G or ovarian ablation (surgery or RT) + TAM</td>
<td>RR OS</td>
<td>0.69 (p=0.3) (recurrence and/or death)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR RFS</td>
<td>0.94 (p =0.8)</td>
<td></td>
</tr>
<tr>
<td>Austrian Breast and Colorectal Cancer Study²¹</td>
<td>1034</td>
<td>G + TAM</td>
<td>60 months</td>
<td>CMF</td>
<td>5yr RFS</td>
<td>76% (CMF); 81% (G + TAM)</td>
<td></td>
</tr>
<tr>
<td>FASG06 (French study)¹⁸</td>
<td>333</td>
<td>Tr + TAM</td>
<td>54 months</td>
<td>FEC₅₀</td>
<td>54-mo DFS</td>
<td>80.9% (FEC₅₀); 91.7% (Tr + TAM) (p=0.12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>54-mo OS</td>
<td>92.9% (FEC₅₀); 97% (Tr + TAM) (p=0.18)</td>
<td></td>
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<tr>
<td>Norwegian study²²</td>
<td>320</td>
<td>G</td>
<td>87 months</td>
<td>TAM</td>
<td>RR OS</td>
<td>1.16 (p=0.42)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR RFS</td>
<td>1.10 (p=0.56)</td>
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</tbody>
</table>
Table 4  Study outcomes (cont'd)

<table>
<thead>
<tr>
<th>Study</th>
<th>N evaluable</th>
<th>Expt</th>
<th>Median follow-up</th>
<th>Comparator</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAM-1 GOGSF</td>
<td>466</td>
<td>CMF</td>
<td>5 yr</td>
<td>D → CMF or CMF → G + TAM or D → CMF → G + TAM</td>
<td>HR RFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.71 (p=0.04) (G + TAM v no G + TAM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86 (p=0.52) (G + TAM v no G + TAM)</td>
</tr>
<tr>
<td>U Pretoria23</td>
<td>145</td>
<td>CMF</td>
<td>not reported</td>
<td>CMF → B</td>
<td>DFS</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>6.2 yr (CMF); 6.8 yr (CMF → B)</td>
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</tbody>
</table>
## Table 5  Approximate cost ($AUD) of treatment

Schedule and duration of treatment as specified in study, where given (nearest $50).

<table>
<thead>
<tr>
<th>Study</th>
<th>LHRH agonist</th>
<th>Pharmaco-economics reported?</th>
<th>Cost of LHRH arm</th>
<th>Cost of tamoxifen arm</th>
<th>Cost of combined endocrine arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZIPP2</td>
<td>Goserelin</td>
<td>No</td>
<td>8200</td>
<td>950</td>
<td>9150</td>
</tr>
<tr>
<td>INT 01016</td>
<td>Goserelin</td>
<td>No</td>
<td>20500</td>
<td>2350</td>
<td>22850</td>
</tr>
<tr>
<td>ZEBRA4</td>
<td>Goserelin</td>
<td>No</td>
<td>8200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBSCG 8</td>
<td>Goserelin</td>
<td>No</td>
<td>8200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TABLE 19</td>
<td>Leuprolein</td>
<td>No</td>
<td>1680</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian Breast Cancer Adjuvant Study 20</td>
<td>Goserelin</td>
<td>No</td>
<td>8200</td>
<td>2350</td>
<td>10550</td>
</tr>
<tr>
<td>Austrian Breast and Colorectal Cancer Study 21</td>
<td>Goserelin</td>
<td>No</td>
<td>12300</td>
<td>2350</td>
<td>14650</td>
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<tr>
<td>FASG06 (French study) 18</td>
<td>Triptorelin</td>
<td>No</td>
<td>1400</td>
<td></td>
<td>1400</td>
</tr>
<tr>
<td>Norwegian study 22</td>
<td>Goserelin</td>
<td>No</td>
<td>8200</td>
<td>950</td>
<td></td>
</tr>
<tr>
<td>MAM-1 GOCSI 7</td>
<td>Goserelin</td>
<td>No</td>
<td>8200</td>
<td>950</td>
<td>9150</td>
</tr>
<tr>
<td>U Pretoria 23</td>
<td>Buserelin</td>
<td>No</td>
<td>Not available in Australia</td>
<td>1400</td>
<td></td>
</tr>
</tbody>
</table>
Table 6  Ongoing clinical trials of LHRH agonists

<table>
<thead>
<tr>
<th>Group</th>
<th>Study</th>
<th>PI</th>
<th>Notes</th>
<th>Randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>German</td>
<td>GABG-IVA</td>
<td>Kaufmann</td>
<td></td>
<td>CMF vs goserelin</td>
</tr>
<tr>
<td>German</td>
<td>GABG-IVB</td>
<td>Kaufmann</td>
<td></td>
<td>Chemo → goserelin vs chemo</td>
</tr>
<tr>
<td>UKCCR</td>
<td></td>
<td>Johnson</td>
<td></td>
<td>TAM vs chemo → TAM vs Ov Supp + TAM</td>
</tr>
<tr>
<td>IBCSG</td>
<td>SOFT</td>
<td>Francis</td>
<td>Pre-menopausal after chemo</td>
<td>Tam vs LHRH + TAM vs LHRH + exemestane</td>
</tr>
<tr>
<td>IBCSG</td>
<td>TEXT</td>
<td>Pagani</td>
<td>Chemo permitted</td>
<td>LHRH + TAM vs LHRH + exemestane</td>
</tr>
<tr>
<td>IBCSG</td>
<td>PERCHE</td>
<td>Nasi</td>
<td></td>
<td>Chemo + LHRH + TAM or exemestane vs LHRH + TAM or exemestane</td>
</tr>
</tbody>
</table>
Appendix 4 List of abbreviations

Time to recurrence – time from randomisation or recurrence

Overall survival – time from randomisation to death of any cause

– Negative

+ Positive

A Doxorubicin, adriamycin

BMD Bone mineral density

C Cyclophosphamide

Chemo Chemotherapy

DFI Disease-free interval

DFS Disease-free survival

Ebc Early breast cancer

EFS Event-free survival

ER– Oestrogen receptor negative

ER+ Oestrogen receptor positive

F 5-fluorouracil

G Goserelin

HR Hazard ratio

Iv intravenous
L leuprorelin
LHRH LHRH agonist
M Methotrexate
N Lymph node
OS Overall survival
Ov Supp Ovarian suppression
PO oral
PR+ Progesterone receptor positive
RFS Recurrence-free survival
sc subcutaneous
TAM/T tamoxifen
Tr triptorelin
QoL Quality of life
Z Goserelin (Zoladex®)
REFERENCES


18. Roche H, Kerbrat P, Bonneterre J et al. Complete hormonal blockade versus chemotherapy in pre-menopausal early-stage breast cancer patients (pts) with positive hormone-receptor (HR+) and 1 – 3 node-positive (N+) tumor: results of the FASG 06 trial. *Proc ASCO* 2000;(abstr 279).


