Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials

LHRH-agonists in Early Breast Cancer Overview group*

Summary

Background Several trials have been done to assess treatment of premenopausal breast cancer with luteinising-hormone-releasing hormone (LHRH) agonists, but results have been inconclusive, especially for patients with hormone-receptor-positive cancer.

Methods We collected individual patients’ data from published trials and did analyses focused on women with tumours positive for oestrogen receptor, progesterone receptor, or both. The main endpoints were recurrence and death after recurrence.

Findings We obtained data for 11,906 premenopausal women with early breast cancer randomised in 16 trials. When used as the only systemic adjuvant treatment, LHRH agonists did not significantly reduce recurrence (28·4% relative reduction, 95% CI consistent with 50·5% reduction to 3·5% increase, p=0·08) or death after recurrence (17·8%, 52·8% reduction to 42·9% increase, p=0·49) in hormone-receptor-positive cancers. Addition of LHRH agonists to tamoxifen, chemotherapy, or both reduced recurrence by 12·7% (2·4–21·9, p=0·02); and death after recurrence by 15·1% (1·8–26·7, p=0·03). LHRH agonists showed similar efficacy to chemotherapy (recurrence 3·9% increase, 7·7% reduction to 17·0% increase; death after recurrence 6·7% reduction, 20·7% reduction to 9·6% increase; both not significant). No trials had assessed an LHRH agonist versus chemotherapy with tamoxifen in both arms. LHRH agonists were ineffective in hormone-receptor-negative tumours.

Interpretation LHRH agonists provide an additional class of agents for treatment of premenopausal women with hormone-receptor-positive breast cancer. Optimum duration of use is unknown.

Introduction Several trials have been done to assess the role of luteinising-hormone-releasing hormone (LHRH) agonists, also known as gonadotropin-releasing hormone agonists, in the adjuvant treatment of premenopausal patients with breast cancer. The trials can be usefully divided into those that assessed the use of LHRH agonists as the only adjuvant treatment, those in which LHRH agonists were used as an addition to tamoxifen, chemotherapy, or both, and those that compared an LHRH agonist (with or without tamoxifen) with a chemotherapy regimen. Results from individual trials have been reported10 but none have been conclusive about the effect of LHRH agonists on time to recurrence, death after recurrence, or overall survival. In particular, although these agents clearly have no value for oestrogen-receptor-negative cancers, their role in patients with hormone-receptor-positive tumours is uncertain.

Some of these trials have been included in an overview of all methods of ovarian ablation;11 this overview included several early trials assessing radiation or surgical menopause, and often oestrogen-receptor status was not available. We did a meta-analysis based on individual patient data to present an updated overview of the evidence, dealing only with trials in which LHRH agonists were assessed, and focusing specifically on results for patients known to be hormone-receptor-positive.

Methods

Data collection
We searched citation databases (PubMed, SpringerLink, with keywords including “LHRH agonist”, “luteinising-hormone-releasing hormone”, “breast cancer”, “adjuvant trials”) and abstracts from major breast cancer meetings to identify all trials that assessed an LHRH agonist in at least one arm of a randomised adjuvant trial for early breast cancer. This search was augmented by use of the database held by the Oxford overview group, by reviewing the references in published reports of known trials, and by discussion with investigators from these trials. To be eligible a study needed to include an assessment of the randomised addition of an LHRH agonist to an adjuvant therapy or a randomised comparison between a systemic treatment and an LHRH agonist. In some trials, ovarian suppression was done with a range of techniques; we only included trials in which more than half the treatments were with an LHRH agonist. The randomised addition of an LHRH agonist was studied in the context of no other systemic adjuvant therapy (five trials), tamoxifen in both arms (five trials), chemotherapy in both arms (seven trials),

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See Comment page 1668
See Perspectives page 1685
Data in parentheses are number randomised, number HR+ randomised.


Table 1: Details of trials included in overview

<table>
<thead>
<tr>
<th>n (HR+)</th>
<th>Recruitment period</th>
<th>Treatment groups*</th>
<th>Entry criteria</th>
<th>Determination of menopausal status</th>
<th>Median follow-up (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG ES188 1536 (1531)</td>
<td>1989-94</td>
<td>CAFx6 (509, 506); CAFx6, gos 5 y (511, 511); CAFx6, gos 5 y+ tam 5 y (516, 514)</td>
<td>N+, HR+, premeno</td>
<td>LMP &lt;4 mo; or LMP &lt;6-12 mo and premeno FSH level; or age &lt;61 y and hyst without BO and premeno FSH level; or previous HRT and age &lt;56 y and premeno FSH after stopping therapy</td>
<td>11.5 (7.5-13.2)</td>
</tr>
<tr>
<td>ZEBRA 1640 (1330)</td>
<td>1990-96</td>
<td>CMFx6 (823, 665); gos 2 y (817, 665)</td>
<td>N+, stage 2, pre/perimeno, age &lt;50 y</td>
<td>FSH &lt;20 IU/mL</td>
<td>6.5 (4.7-8.1)</td>
</tr>
<tr>
<td>ABCSG 5 1037 (1008)</td>
<td>1990-99</td>
<td>CMFx6 (525, 511); gos 3 y+ tam 5 y (512, 497)</td>
<td>Stage 1 or 2, HR+, premeno</td>
<td>LMP &lt;12 mo</td>
<td>8.9 (6.1-10.9)</td>
</tr>
<tr>
<td>IBCSG VIII 1109 (857)</td>
<td>1990-99</td>
<td>CMFx6 (360, 280); CMFx6, gos 18 mo (357, 281); gos 2 y (346, 265); no treatment (46, 31)</td>
<td>N-, stage T1-3, pre/perimeno</td>
<td>Age &gt;52 y and LMP &lt;1 y; or age ≥52 y and LMP &lt;3 y; or age ≥55 y and hyst without BO; FSH for doubtful cases</td>
<td>8.0 (5.9-10.2)</td>
</tr>
<tr>
<td>GABG IV-A-93 771 (764)</td>
<td>1993-2001</td>
<td>CMFx3 (378, 374); gos 2 y (393, 390)</td>
<td>N-, HR+, premeno</td>
<td>LMP &lt;6 mo; or FSH ≥20 IU/mL; or LH &gt;50 pg/mL</td>
<td>4.7 (3.0-6.4)</td>
</tr>
<tr>
<td>ZIPP STOCKHOLM 926 (591)</td>
<td>1990-97</td>
<td>Control (234, 141); tam 2 y (231, 153)</td>
<td>Age &lt;50 y or premeno, age ≥50 y</td>
<td>LMP &lt;6 mo</td>
<td>5.4 (4.0-7.2)</td>
</tr>
<tr>
<td>TABLE 589 (570)</td>
<td>1995-98</td>
<td>CMFx6 (295, 286); leuprolide 2 y (294, 284)</td>
<td>Stage T1-3, N+, HR+, pre/perimeno</td>
<td>Premenopausal FSH levels</td>
<td>5.9 (4.1-6.6)</td>
</tr>
<tr>
<td>ZIPP CRC &lt;50 1191 (446)</td>
<td>1987-99</td>
<td>Control (137, 141); tam 2 y (140, 142); CMFx6 (157, 159)</td>
<td>Age &lt;50 y or premeno, stage 1-2</td>
<td>LMP &lt;6 mo</td>
<td>9.3 (6.3-11.8)</td>
</tr>
<tr>
<td>GABG IV-B-93 776 (308)</td>
<td>1993-2000</td>
<td>CMFx3 (299, 96); CMFx3, gos 2 y (297, 107); ECx4+CMFx3 (93, 54); ECx4+CMFx3, gos 2 y (87, 51)</td>
<td>N+, HR+, premeno, age ≥50 y</td>
<td>LMP &lt;1 y and no previous hyst</td>
<td>7.7 (5.8-9.4)</td>
</tr>
<tr>
<td>FASG 06 331 (325)</td>
<td>1990-98</td>
<td>FECx6 (168, 155); tripletrolle 3 y+ tam 3 y (165, 160)</td>
<td>N+, HR+, premeno, age ≥50 y</td>
<td>LMP &lt;3 mo; or E2 &gt;60 pmol/mL; or FSH &gt;30 IU/mL</td>
<td>8.3 (5.4-10.5)</td>
</tr>
<tr>
<td>FNCLCC 490 (300)</td>
<td>1989-96</td>
<td>Chemo (249, 146); chemo, tripletrolle 3 y (241, 154)</td>
<td>N+ or grade 2-3 tumours, premeno</td>
<td>Still actively menstruating or LMP &lt;1 y, or Hyst and age &lt;55 y; or hyst and FSH &lt;50 IU/mL</td>
<td>9.2 (7.4-11.3)</td>
</tr>
<tr>
<td>GROCTA 02 244 (244)</td>
<td>1989-97</td>
<td>CMFx6 (120, 120); ovarian suppression (gos 2 y, irradiation, surgery)+ tam 5 y (124, 124)</td>
<td>ER+, pre/perimeno</td>
<td>Premenopausal, age &lt;50 y</td>
<td>7.8 (5.7-10.4)</td>
</tr>
<tr>
<td>ZBRC 002 207 (206)</td>
<td>1994-98</td>
<td>Tam 2 y (94, 94); gos 2 y (93, 92); gos 2 y+ tam 2 y (457, 175); tam 2 y (463, 192)</td>
<td>ER+, stage 1-3a, premeno, age ≤50 y</td>
<td>Premenopausal status</td>
<td>5.1 (3.0-5.2)</td>
</tr>
<tr>
<td>ZIPP GIOVIO 382 (195)</td>
<td>1991-96</td>
<td>Control (50, 50); gos 2 y (46, 48); gos 2 y+ tam 2 y (104, 103); tam 2 y (88, 88)</td>
<td>Age ≥50 y, stage 1-3</td>
<td>LMP &lt;6 mo</td>
<td>4.9 (3.5-6.7)</td>
</tr>
<tr>
<td>MAM-1 GOCI 466 (194)</td>
<td>1991-96</td>
<td>CMFx6 (114, 53); CMFx6, gos 2 y+ tam 2 y (120, 48); adriamycin, CMFx6 (192, 42), adriamycin, CMFx6, gos 2 y+ tam 2 y (113, 51)</td>
<td>N+, premeno</td>
<td>LMP &lt;6 mo before randomisation, or premeno FSH, LH, and E2 serum levels in women &lt;50 y with previous hyst without BO</td>
<td>5.2 (3.0-6.9)</td>
</tr>
<tr>
<td>ZIPP SE SWEDEN 211 (153)</td>
<td>1989-98</td>
<td>Control (31, 9); gos 2 y (8, 2); gos 2 y+ tam 2 y (94, 68); tam 2 y (98, 74)</td>
<td>Age ≥50 y, stage 1-3</td>
<td>LMP &lt;6 mo</td>
<td>5.0 (3.6-6.8)</td>
</tr>
</tbody>
</table>


or chemotherapy and tamoxifen in both arms (four trials). A second set of trials assessed a chemotherapy regimen versus an LHRH agonist (four trials), and a third group assessed chemotherapy versus an LHRH agonist combined with tamoxifen (three trials). No trials had assessed the question of chemotherapy versus an LHRH agonist, with tamoxifen in both arms.

For trials with more than two treatment arms, an equal valid pairwise comparison was considered separately. In all trials, treatments were given in an unblinded open-label fashion. We focused on patients who were known to have tumours positive for oestrogen receptor, progesterone receptor, or both, designated hormone-receptor-positive. Results for patients whose tumours were hormone-receptor-negative or oestrogen-negative and progesterone-negative are presented briefly.

Patients with unknown receptor status were not included in the overview. The extent of such missing data varied between trials, but was mainly due to the differences in prevailing practice in different centres and countries, and at different calendar times, leading to different protocol requirements. This variation was unlikely to present a selection bias.

For each patient, information was sought on oestrogen-receptor or progesterone-receptor positivity, nodal status, tumour size, and age at randomisation. We also sought information on the date of randomisation, the allocated treatment, and the dates of first recurrence (which included...
any contralateral breast cancer, local or regional recurrence, or distant recurrence), death, and last follow-up. The date of distant recurrence, when it occurred as a second event, was also requested, but was not always available. The data were checked for internal consistency with published results and for outliers, and were updated or amended as necessary through correspondence with the trialists.

### Statistical analyses

Comparisons were made on an intention-to-treat basis within the subgroups of hormone-receptor-positive (ie, oestrogen-receptor positive or progesterone-receptor positive, or both) and hormone-receptor-negative (ie, oestrogen-receptor negative and progesterone-receptor negative, or oestrogen-receptor negative and progesterone-receptor positive).
Articles

Figure 1: Recurrence and death after recurrence in trial subgroups
Sys = systemic therapy. LHRH = LHRH agonist. Tam = tamoxifen. Chemo = chemotherapy.

progesterone-receptor unknown) patients. Cutoffs for hormone-receptor positivity were as used in the original trials. Log hazard ratios and their variance were computed separately for each trial and a fixed-effect estimate of the overall log hazard ratio and its variance were calculated with the inverse variance-weighted method. The analysis was done in Stata (version 9.2) using the meta command. Results are presented as changes in hazard rates with 95% CI and two-sided p values. In trials with three or more arms, some patients contributed to more than one comparison, but these comparisons were always in separate sub-categories of trials. The primary endpoints analysed were any recurrence and death after recurrence. Data were shown as proportion of women with an event, using Kaplan-Meier methods. In both cases women who were recorded as having died without recurrence were censored at the date of death. For completeness, disease-free survival and overall survival were also reported. Recurrence was defined as the first reappearance of breast cancer at any site (local or regional, contralateral, or distant). In some trials only the first recurrence was recorded, so that the existence and time of a distant recurrence would not be known if it was preceded by a local recurrence for these trials; therefore, we were unable to assess the time to distant recurrence separately.

Formal interaction tests were done by examining the change in likelihood ratio χ² when an interaction term was added to a proportional hazard model stratified by hormone-receptor positivity. The key parameters for the included trials are shown in table 1. Goserelin was used in one (389). Most of the chemotherapy given was CMF-based (61% of randomised chemotherapy, 3858 patients; 66% of all chemotherapy, 4966 patients) but anthracycline-based chemotherapy was used for 38% (2410 patients) of the patients who received randomised chemotherapy (32% of all chemotherapy), including 412 patients (7% of randomised chemotherapy, 5% of all chemotherapy) who had anthracycline-based chemotherapy followed by CMF. No patients received taxanes. Duration of LHRH treatment was 2 years in

# Table 4: Percentage change in hazard ratios (95% CI) for outcomes in women with hormone-receptor-positive cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>Recurrence</th>
<th>Recurrence or death</th>
<th>Death after recurrence</th>
<th>All deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sys LHRH</td>
<td>-28.4 (-50.5 to 3.5), p=0.08</td>
<td>-25.2 (-40.6 to -5.8), p=0.01</td>
<td>-17.8 (-52.6 to 42.9), p=0.49</td>
<td>-22.9 (-44.1 to 6.4), p=0.11</td>
</tr>
<tr>
<td>No sys LHRH+tam</td>
<td>-58.4 (-72.9 to -36.0), p&lt;0.0001</td>
<td>-60.6 (-73.5 to -39.6), p&lt;0.0001</td>
<td>-46.6 (-70.5 to -3.4), p=0.04</td>
<td>-49.4 (-70.8 to -12.2), p=0.02</td>
</tr>
<tr>
<td>Chemo+LHRH</td>
<td>-14.5 (-32.7 to 8.6), p=0.20</td>
<td>-15.9 (-31.8 to 8.7), p=0.21</td>
<td>-15.9 (-40.7 to 19.4), p=0.33</td>
<td>-13.7 (-31.6 to 20.3), p=0.39</td>
</tr>
<tr>
<td>Chemo+LHRH</td>
<td>-11.7 (-22.8 to 8.3), p=0.07</td>
<td>-11.0 (-22.0 to 1.5), p=0.08</td>
<td>-12.9 (-26.5 to 2.2), p=0.11</td>
<td>-11.5 (-24.8 to 4.0), p=0.14</td>
</tr>
<tr>
<td>Chemo+LHRH</td>
<td>-15.9 (-42.4 to 22.6), p=0.37</td>
<td>-12.8 (-39.7 to 25.9), p=0.46</td>
<td>-32.6 (-60.1 to 13.7), p=0.14</td>
<td>-30.3 (-57.4 to 13.9), p=0.05</td>
</tr>
<tr>
<td>Chemo+LHRH</td>
<td>-12.2 (-22.5 to -0.3), p=0.04</td>
<td>-12.2 (-21.6 to 0.5), p=0.06</td>
<td>-15.0 (-27.6 to -0.1), p=0.04</td>
<td>-13.6 (-26.0 to 0.9), p=0.07</td>
</tr>
<tr>
<td>Any sys LHRH</td>
<td>-11.8 (-21.0 to -1.6), p=0.02</td>
<td>-11.8 (-21.0 to -1.6), p=0.02</td>
<td>-15.1 (-26.7 to -1.8), p=0.03</td>
<td>-13.6 (-24.9 to 0.6), p=0.04</td>
</tr>
<tr>
<td>Chemo+LHRH+LHRH</td>
<td>-26.7 (-38.7 to -12.3), p&lt;0.001</td>
<td>-23.8 (-35.9 to -9.4), p=0.002</td>
<td>-24.4 (-39.0 to -6.4), p=0.01</td>
<td>-19.8 (-36.0 to -1.7), p=0.03</td>
</tr>
<tr>
<td>Chemo+LHRH+LHRH</td>
<td>-10.1 (-25.0 to 7.8), p=0.25</td>
<td>-11.3 (-25.0 to 5.8), p=0.18</td>
<td>-11.1 (-31.5 to 15.0), p=0.37</td>
<td>-12.8 (-31.6 to 11.1), p=0.27</td>
</tr>
</tbody>
</table>

17 trials were eligible for this meta-analysis. For one small trial from Pretoria, South Africa, no investigator could be contacted and data were not available. This trial involved the randomised addition of buserelin to cyclophosphamide-methotrexate-5-fluorouracil (CMF) in 66 women. Therefore 16 trials were available for the overview, with 34 pairwise comparisons identified. Another recent trial, the Adjuvant Breast Cancer (ABC) international trial, was not eligible because in most cases, ovarian suppression was done by radiation-induced ablation or by surgery. The key parameters for the included trials are shown in table 1. Goserelin was used in 13 trials (10450 patients), triptorelin in two (821), and leuprolrein in one (589). Most of the chemotherapy given was CMF-based (61% of randomised chemotherapy, 3858 patients; 66% of all chemotherapy, 4966 patients) but anthracycline-based chemotherapy was used for 38% (2410 patients) of the patients who received randomised chemotherapy (32% of all chemotherapy), including 412 patients (7% of randomised chemotherapy, 5% of all chemotherapy) who had anthracycline-based chemotherapy followed by CMF. No patients received taxanes. Duration of LHRH treatment was 2 years in
most trials, but 18 months, 3 years, or 5 years were also used. Treatment duration was 3 years in both trials using triptorelin.

The E5188 trial was a three-arm trial started by the Eastern Cooperative Oncology Group (ECOG) in 1989 to compare six cycles of cyclophosphamide-doxorubicin-5-fluourouracil (CAF), six cycles of CAF followed by 5 years of goserelin, or six cycles of CAF followed by 5 years of goserelin plus tamoxifen in pre-menopausal women with hormone-receptor-positive, node-positive breast cancer.

The Zoladex Early Breast Cancer Research Association (ZEBRA) study was an international trial that started in 1990 and assessed 2 years of goserelin compared with six cycles of CMF in premenopausal or perimenopausal women aged 50 years or younger, with node-positive, stage 2 breast cancer, who had received no previous systemic treatment.

The Austrian Breast and Colorectal Cancer Study Group (ABCSG) 05 trial was started in 1990 and assessed six cycles of CMF every 28 days compared with goserelin for 3 years plus tamoxifen for 5 years in premenopausal women with hormone-receptor-positive, stage 1 or 2 breast cancer.

The Zoladex in Pre-menopausal Patients (ZIPP) study was a combination of four multicentre trials (STOCKHOLM, CRC<50, SE SWEDEN, GIVIO) done in premenopausal women or women younger than 50 years with operable stage 1 or 2 breast cancer. These trials were designed together to facilitate a subsequent preplanned overview. Patients were selected for chemotherapy according to local criteria (mainly those at increased risk of recurrence due to the presence of involved nodes) and the type of chemotherapy given was also determined locally (perioperative cyclophosphamide or six cycles of CMF chemotherapy were recommended in the protocol, but some centres used a standard 5-fluorouracil-epirubicin-cyclophosphamide [FEC] regimen). 50% of patients (459 patients) from the STOCKHOLM trial had CMF before randomisation. In the CRC<50 trial, 38% of patients (449 patients) had chemotherapy (CMF for 84%, 377) before randomisation, 58% (689) had elective tamoxifen and 4% (50 patients) were not given tamoxifen electively. In GIVIO, 61% of patients (232) had CMF before randomisation. In SE SWEDEN, 20% (43) had CMF before randomisation, and 81% (171) had elective tamoxifen. The main randomisation was to goserelin for 2 years, tamoxifen for 2 years, the combination of goserelin and tamoxifen for 2 years, or no further endocrine treatment in a 2x2 design. However, some patients received elective tamoxifen (or not) according to local policies, and were only randomised to goserelin or not.
The International Breast Cancer Study Group (IBCSG) trial VIII was initially a four-arm trial to compare no systemic adjuvant treatment, six courses of CMF, 2 years of goserelin, or six courses of CMF followed by 18 months of goserelin, in node-negative, premenopausal or perimenopausal women. The no-treatment arm was closed early after recruiting 46 patients. These patients were compared only with other patients randomised before the closure date of the arm (March 26, 1992).

The German Adjuvant Breast Cancer Group (GABG) began the randomised, multicentre trial IV-A-937 in 1993 to compare three cycles of CMF with 2 years of goserelin in node-negative premenopausal women with hormone-receptor-positive breast cancer.

The Takeda Adjuvant Breast Cancer Study with Leuprorelin Acetate (TABLE) study was set up in 1995 to compare six cycles of CMF with 2 years of leuprorelin in hormone receptor-positive, node-positive, premenopausal and perimenopausal women with stage T1-3 breast cancer.

The GABG trial IV-B-93 was started in 1993 to assess goserelin for 2 years compared with no further treatment after four cycles of epirubicin-cyclophosphamide (EC) followed by three cycles of CMF for patients with four to nine positive nodes, and after three cycles of CMF for patients with three or fewer positive nodes, in premenopausal women with breast cancer. Most of these patients were hormone-receptor-negative. The trial started with hormone-receptor-negative patients only and was opened to hormone-receptor-positive patients when the ZEBRA trial was closed.

The French Adjuvant Study Group 06 (FASG06), which began in 1990, compared six cycles of FEC with 3 years of a combination of triptorelin and tamoxifen in premenopausal node-positive women younger than 50 years.

The Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) study was set up in 1989 to evaluate the role of ovarian suppression in the treatment of pre-menopausal women with either axillary node involvement or histological grade 2 or 3 tumours who had received adjuvant chemotherapy (60% [294 patients] anthracycline-based, 35% [170] CMF, 5% [26] other or none). The anthracycline-treated patients were assessed as a separate stratum in the analysis. The patients were randomised to receive 3 years of triptorelin or no further treatment after the completion of chemotherapy.

The Italian Breast Cancer Adjuvant Study Group 02 (GROCTA02) trial was set up in 1989 and assessed six cycles of CMF compared with the combination of tamoxifen (for 5 years) and ovarian suppression in premenopausal and perimenopausal women with...
oestrogen-receptor-positive tumours. For most of the patients (79%, 87), ovarian suppression was achieved with goserelin but 25% (31) had irradiation and 5% (six) had surgery. All randomised patients were included in our analysis to avoid bias.

The Japan-Zoladex Breast Cancer Study Group trial-B (ZXBC1002)13 was a three-arm trial comparing 2 years of tamoxifen, 2 years of goserelin, and the combination of tamoxifen and goserelin for 2 years in premenopausal oestrogen-receptor-positive women, who were younger than 50 years with a stage 1, 2, or 3a breast cancer. Only the first and last arms were included in our analysis. 30% of the patients (61) had mitomycin C before randomisation.

The MAM-1 Gruppo Oncologico Centro-Sud-Isole (GOCSI) trial14 had a factorial 2×2 design in node-positive pre-menopausal women. This study compared two chemotherapy regimens (CMF, or doxorubicin followed by CMF), each with or without goserelin and tamoxifen combined for 2 years. The chemotherapy allocations were treated as separate strata in the analysis.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Baseline factors (age, body-mass index [BMI], tumour size, nodal status, oestrogen-receptor status, and progesterone-receptor status) for the trials are shown in table 2. No imbalance between treatment arms for any of these factors was found at the 1% significance level.

11906 women were randomised in the 16 trials we assessed. The median follow-up was 6·8 years (IQR 4·6–9·3) with a total of 83 933 patient-years. We focused on the 9022 hormone-receptor-positive patients, who comprised 75·8% of all randomised patients. Of these, 8278 (91·8%) were oestrogen-receptor-positive; the remainder were oestrogen-receptor-negative but progesterone-receptor-positive. As expected, age, nodal status, and tumour size were significant independent prognostic factors (table 3). Obesity (BMI>30 kg/m²) was also an independent prognostic factor in the univariate and multivariate models (table 3).

The summarised results for recurrence, disease-free survival, death after recurrence, and overall survival are...
shown in table 4. Figure 1 shows results for recurrence and death after recurrence.

The effects on recurrence and death after recurrence of the use of an LHRH agonist as the sole systemic therapy (n=338) are shown overall in figure 2 and by trial in figure 3. Use of an LHRH agonist compared with no systemic treatment did not have a significant effect on recurrence (28·4% relative reduction in hazard rate, 95% CI consistent with 50·5% reduction to 3·5% increase, p=0·08) or on death after recurrence (17·8%, 52·8% reduction to 42·9% increase, p=0·49), or death from any cause (22·9%, 44·1% reduction to 6·4% increase, p=0·11). However, the number of patients included in this comparison was very small.

When an LHRH agonist and tamoxifen were used together in the absence of other systemic therapy (n=407), significant reductions were noted for recurrence (58·4%, 95% CI 36·0–72·9, p<0·0001), death after recurrence (46·6%, 3·4–70·5, p=0·04), and death from any cause (49·4%, 12·2–70·8, p=0·02). The effects on recurrence and death after recurrence of the addition of an LHRH agonist to tamoxifen (n=1013) are shown overall in figure 4 and by trial in figure 5. The addition of an LHRH agonist to tamoxifen did not significantly reduce the hazard rates for recurrence (14·5% reduction, 95% CI 32·7% reduction to 8·6% increase, p=0·20), death after recurrence (15·9%, 40·7% reduction to 19·4% increase, p=0·33), or death from any cause (13·7%, 38·1% reduction to 20·3% increase, p=0·39).

The effects on recurrence and death after recurrence of the addition of an LHRH agonist to chemotherapy, with or without tamoxifen (n=2741), are shown overall in figure 6 and by trial in figure 7. This approach significantly reduced the hazard rate for recurrence by 12·2% (95% CI 0·3–22·6, p=0·04) and the hazard rate for death after recurrence by 15·0% (0·1–27·6, p=0·04); the hazard rate for any death was not significantly reduced (13·7% reduction, 26·0% reduction to 0·9% increase, p=0·07).

The addition of an LHRH agonist to chemotherapy, without tamoxifen in either arm (n=2376), did not significantly reduce the hazard rate for recurrence (11·7% reduction, 95% CI 22·8% reduction to 1·0% increase, p=0·07), death after recurrence (12·9% reduction, 26·5% reduction to 3·2% increase, p=0·11), or death from any cause (11·5% reduction, 24·8% reduction to 4·2% increase, p=0·14).

The addition of an LHRH agonist to chemotherapy plus tamoxifen (n=365) did not significantly reduce rate of recurrence (15·9% reduction, 95% CI 42·4% reduction to 22·6% increase, p=0·37), death after recurrence...
(32·6%, 60·1% reduction to 13·7% increase, p=0·14), or death from any cause (30·3% reduction, 57·4% reduction, to 13·9% increase, p=0·15).

The addition of an LHRH agonist to tamoxifen, chemotherapy, or both (n=3754) significantly reduced the hazard rate by 12·7% (95% CI 2·4–21·9, p=0·02) for recurrence, by 15·1% (1·8–26·7, p=0·03) for death after recurrence, and by 13·6% (0·6–24·9, p=0·04) for death from any cause.

When both an LHRH agonist and tamoxifen were added to chemotherapy (n=1210), a significant 26·7% reduction for recurrence was noted (95% CI 12·3–38·7, p=0·001), with a significant 24·4% reduction in death after recurrence (6·4–39·0, p=0·01) and a significant 19·8% reduction in death from any cause (1·7–34·6, p=0·03).

The effects on recurrence and death after recurrence of the use of chemotherapy compared with an LHRH agonist (n=3184) are shown overall in figure 8 and by trial in figure 9. Allocation to an LHRH agonist as opposed to chemotherapy produced similar absolute rates of recurrence (3·9% increase, 95% CI 7·7% reduction to 17·0% increase, p=0·52), deaths after recurrence (6·7% reduction, 20·7% reduction to 9·6% increase, p=0·40), and deaths from any cause (14·9% reduction, 27·7% reduction to 0·1% increase, p=0·05).

The effects on recurrence and death after recurrence of the use of chemotherapy versus an LHRH agonist plus tamoxifen (n=1577) are shown overall in figure 10 and by trial in figure 11. The combination of an LHRH agonist plus tamoxifen compared with chemotherapy without tamoxifen did not significantly change the hazard ratio for recurrence (10·1% reduction, 95% CI 25·0% reduction to 7·8% increase, p=0·25), for death after recurrence (11·1% reduction, 31·3% reduction to 15·0% increase, p=0·37), or for death from any cause (13·0% reduction, 32·4% reduction to 12·0% increase, p=0·28).

Results are shown separately for women aged 40 years or younger and those older than 40 years in table 5. We noted no significant effect of age, except for the addition of an LHRH agonist to chemotherapy with or without tamoxifen, for which an interaction test was significant for recurrence (p=0·046), but not significant for death after recurrence; in women aged 40 years or younger, the addition of an LHRH agonist significantly reduced rates for recurrence by 25·2% (7·7–39·4, p=0·01), death after recurrence by 28·3% (6·8–44·9, p=0·01), and all deaths by 27·4% (6·5–43·6, p=0·01). However, we noted no significant difference for women older than 40 years. Figure 12 shows the contribution of the individual trials for the addition of an LHRH-agonist to chemotherapy.

Figure 10: Chemotherapy versus LHRH agonist plus tamoxifen

Figure 11: Contributions of individual trials for chemotherapy versus LHRH agonist plus tamoxifen
(with or without tamoxifen) by age. Interaction tests were also significant when age was treated as a continuous variable (p=0.043 for recurrence, not significant for death after recurrence). When age was divided into 5-year groups, the largest effect was seen in women aged 35 years or younger (HR 0.66); a significant effect was seen for women aged 35–39 years (0.77), but not for those aged 40–44 years (0.96), 45–49 years (1.03) or 50 years and older (0.85).

Only 1681 patients were known to have negative or poor oestrogen-receptor status and either negative or poor (925) or unknown (756) progesterone-receptor status. In these patients, treatment with an LHRH agonist was not very useful (table 6). In general, addition of an LHRH agonist to any other treatment did not affect rates of recurrence or death after recurrence rates. Use of an LHRH agonist instead of chemotherapy resulted in a significantly increased recurrence rate (67.7%, 95% CI 22.2–129.9, p=0.001) and similar rates of breast-cancer-specific survival (42.2% increased rate of death after recurrence, 1.7% reduction to 105.9% increase, p=0.06), and overall survival (37.4% increase, 4.0% reduction to 96.6% increase, p=0.08).

Discussion

The results of our analysis show that LHRH agonists provide an effective additional class of agents for the treatment of premenopausal women with hormone-sensitive breast cancer. In the few patients who participated in the assessment of an LHRH agonist alone compared with no systemic therapy, LHRH agonists did not significantly reduce rates of recurrence, although the apparent effect size was large. The size of the effect was consistent with that of earlier trials of ovarian ablation as the only adjuvant treatment.15 Large significant effects were seen when LHRH agonists plus tamoxifen were compared with no other systemic therapy, but these effects were partly due to tamoxifen.

Larger groups of patients participated in trials of an LHRH agonist compared with chemotherapy, in which...
LHRH agonists were about equally as effective as the chemotherapy regimens used. LHRH agonists also showed a small additional benefit when used after chemotherapy, either alone or with tamoxifen, in women aged 40 years or younger, in whom chemotherapy is less likely to induce permanent amenorrhea than in older women. The occurrence of this outcome might now be more common with the use of modern, non-CMF-based chemotherapy, for which permanent amenorrhea after treatment seems to be less common.18 The effect size of adding an LHRH agonist was similar in those with or without tamoxifen, but few patients took part in trials in which tamoxifen was given in both arms, and the benefit of an LHRH agonist in this context is less certain. The occurrence of this outcome might now be more common with the use of modern, non-CMF-based chemotherapy, for which permanent amenorrhea after treatment seems to be less common.18 The effect size of adding an LHRH agonist was similar in those with or without tamoxifen, but few patients took part in trials in which tamoxifen was given in both arms, and the benefit of an LHRH agonist in this context is less certain.

Table 6: Percentage change in hazard ratios (95% CI) for outcomes in women with hormone-receptor-negative cancer

<table>
<thead>
<tr>
<th>n</th>
<th>Recurrence</th>
<th>Recurrence or death</th>
<th>Death after recurrence</th>
<th>All deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sys±LHRH</td>
<td>144</td>
<td>-37·6 (–63·4 to 6·7), p=0·09</td>
<td>-10·9 (–56·1 to 81·0), p=0·79</td>
<td></td>
</tr>
<tr>
<td>No sys±(LHRH+tam)</td>
<td>178</td>
<td>-25·7 (–56·6 to 27·1), p=0·28</td>
<td>-37·6 (–70·2 to 30·7), p=0·21</td>
<td></td>
</tr>
<tr>
<td>Tam±LHRH</td>
<td>427</td>
<td>-0·6 (–27·5 to 36·3), p=0·97</td>
<td>-13·0 (–42·0 to 30·5), p=0·50</td>
<td></td>
</tr>
<tr>
<td>Chemo±LHRH</td>
<td>777</td>
<td>18·5 (–58·2 to 67·7), p=0·19</td>
<td>16·7 (–1·7 to 39·0), p=0·17</td>
<td></td>
</tr>
<tr>
<td>Chemo±tamu±LHRH</td>
<td>197</td>
<td>18·3 (–26·1 to 69·4), p=0·48</td>
<td>22·1 (–31·3 to 116·8), p=0·50</td>
<td></td>
</tr>
<tr>
<td>(Chemo±tam)±LHRH*</td>
<td>974</td>
<td>18·5 (–5·2 to 48·1), p=0·14</td>
<td>17·9 (–10·7 to 55·7), p=0·25</td>
<td></td>
</tr>
<tr>
<td>Any sys±LHRH†</td>
<td>1401</td>
<td>11·7 (–6·9 to 34·1), p=0·23</td>
<td>7·0 (–14·9 to 34·6), p=0·56</td>
<td></td>
</tr>
<tr>
<td>Chemo±(LHRH+tam)</td>
<td>76</td>
<td>-15·8 (–56·9 to 64·4), p=0·61</td>
<td>-15·8 (–56·9 to 64·4), p=0·61</td>
<td></td>
</tr>
<tr>
<td>Chemo±LHRH</td>
<td>316</td>
<td>67·7 (22·2 to 129·9), p=0·001</td>
<td>62·1 (17·9 to 122·8), p=0·003</td>
<td></td>
</tr>
</tbody>
</table>

Figure 12: Contributions of individual trials for addition of LHRH agonist to chemotherapy with or without tamoxifen by age

LHRH=LHRH agonist. Tam=tamoxifen. Chemo=chemotherapy.
similar sized benefit was seen for the addition of an LHRH agonist to tamoxifen alone, but this was not significant by itself. Regimens that used an LHRH agonist plus tamoxifen were highly effective when used alone or when added to chemotherapy, undoubtedly owing in part to the known effectiveness of tamoxifen, although the use of an LHRH agonist plus tamoxifen was not significantly better than chemotherapy alone. No trials had compared an LHRH agonist against chemotherapy with tamoxifen in both arms, and this important question needs to be addressed.

Most trials used a CMF-based regimen, but anthracycline-based regimens were used in ECOG, FASG 06, and parts of the GOCSI and FNCLCC trials, and we found no evidence that results of adding an LHRH agonist differed between these regimens. For many of the trials, only node-positive patients were entered. In the ZIPP and ZXBC1002 trials, the use of chemotherapy was determined locally and only the endocrine treatments were randomised, whereas for the other trials, the use of a specific chemotherapy regimen was fully specified and part of the trial design. No trials directly compared an LHRH agonist with anthracycline-based chemotherapy, although the FASG 06 trial compared FEC with 3 years of the combination of triptorelin and tamoxifen, and showed that both treatments provided similar outcomes for disease-free survival and overall survival in hormone-receptor positive patients. Most trials used goserelin as the LHRH agonist (88% of all use), but the use of triptorelin or leuprorelin did not seem to lead to any difference in results.

The magnitude of the effect on death after recurrence was largely similar to that for recurrence, although the confidence intervals were wider because the numbers of events were small. The number of deaths without recurrence was small and similar in arms with and without LHRH agonists, so that results for overall survival were very similar to those for death after recurrence.

This overview substantially updates and refines the previous one based on data up to the year 2000. We dealt only with trials that used LHRH agonists, and focused specifically on results for patients known to be hormone-receptor-positive. The number of patients included in this key group was substantially larger than that available in the previous overview. A report for the ABC trial, in which almost all ovarian suppression was by surgery or radiotherapy, has given qualitatively similar results when restricted to oestrogen-receptor-positive patients, in whom the hazard ratio for relapse when adding ovarian ablation to 5 years of tamoxifen with or without chemotherapy was 0.84 (0.59–1.20; not significant). We considered all randomised premenopausal women, even if they were older than 50 years. The number of women in this clinically relevant category in our overview is more than twice as many as in the previous report. We did not include trials of ovarian ablation by either surgery or radiation, but most of these were old trials in which hormone-receptor data were not available, and would therefore not be informative for analyses stratified by hormone-receptor status. Our results broadly support those of the previous analyses, but also show other important details. Of particular importance is the benefit of LHRH agonists after chemotherapy in women younger than 40 years, but not in older premenopausal women, and the equivalence of LHRH agonists with chemotherapy in hormone-receptor-positive cancers, but not in hormone-receptor-negative ones.

In view of the overall similarity in efficacy between treatments, side-effect profiles are very important in choosing which type of treatment to offer. All the trials were open label, so biases in the assessment of side-effects are possible. In the ZIPP CRC study, 26% of patients reported hot flushes with goserelin alone and 44% with goserelin plus tamoxifen, compared with no women in the control arm and 17% of those who only received tamoxifen. In the ZEBRA trial, overall quality of life was better with goserelin than CMF during the active phase of chemotherapy, but little difference was noted after 1 year. Hormonal side-effects were increased with goserelin during the 24 months of treatment with an LHRH agonist, but by 36 months were higher in patients treated with CMF, because of a greater proportion with permanent amenorrhoea. Similar results have been reported for the IBCSG trial VIII study. The ECOG trial showed increases in weight gain, hypertension, diabetes, and hot flushes when 5 years of goserelin were added afterCAF, although one should note that these assessments, as all the others on side-effects, were not blinded to treatment arm.

Other important questions remain. In particular, whether adding an LHRH agonist is only useful when amenorrhoea is not achieved with chemotherapy. Some trials have shown a worse outcome after chemotherapy in women who did not experience amenorrhoea after chemotherapy and these women could be the ones who benefit most from the addition of an LHRH agonist. Also, a more detailed assessment of the value of an LHRH agonist according to oestrogen and progesterone receptor status is needed. More recent trials (ABCSG trial 12, SOFT, TEXT, PROMISE) are investigating the use of more complete suppression with an LHRH agonist in combination with an aromatase inhibitor.

Contributors
The writing committee accept full responsibility for the overall content of this report. They all participated in the design and conduct of the study and in evaluation and interpretation of the data, and all contributed to the preparation of this report.

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References


Conflict of interest statement

JC is a statistical consultant for AstraZeneca, but these activities are unrelated to the drugs under consideration in this overview. The members of the writing committee declare that we have no other conflict of interest.