National Institute for Health and Care Excellence

Early and locally advanced breast cancer: diagnosis and management

[Q] Ovarian function suppression

NICE guideline NG101
Evidence review underpinning recommendation 1.7.2 and research recommendations in the NICE guideline

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Draft for consultation

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ISBN:

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1.1 Review question

What is the clinical and cost-effectiveness of ovarian function suppression combined with other endocrine therapy using tamoxifen or an aromatase inhibitor in people with oestrogen receptor positive invasive breast cancer that is local or locally advanced who have female reproductive organs and are premenopausal or perimenopausal?

1.1.1 Introduction

The current advice focuses on considering ovarian function suppression combined with tamoxifen or an aromatase inhibitor as an endocrine therapy, as part of the treatment for breast cancer, in premenopausal people with female reproductive organs and with oestrogen receptor (ER) positive early or locally advanced invasive breast cancer. (When we mention people with female reproductive organs, we mean this to cover women, trans men and non-binary people who currently have ovaries.) The recommendations are based on evidence from studies where ovarian function suppression was combined with tamoxifen as an endocrine therapy. New evidence identified by the 2023 surveillance review indicates that ovarian function suppression combined with an aromatase inhibitor may be a suitable or better alternative than ovarian function suppression combined with tamoxifen. The evidence in this area will be reviewed as part of this update. This update will not look at ovarian function suppression as a means of preserving fertility during treatment for breast cancer.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	**Inclusion:** • Adults (18 and over) with invasive ER positive breast cancer and female reproductive organs who are premenopausal or perimenopausal. The invasive breast cancer is of any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0). **Exclusion:** Adults (18 and over) with: • invasive ER positive breast cancer and female reproductive organs who are postmenopausal • invasive breast cancer that is not ER positive. • metastatic breast cancer (covered by CG81 currently). • newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Paget's disease of the breast with no invasive component.
Interventions	• Ovarian function suppression combined with other endocrine therapy (either an aromatase inhibitor* or tamoxifen) Ovarian function suppression using:

	○ Luteinising-hormone releasing hormone (LHRH) agonists of interest: buserelin, goserelin, leuprorelin, nafarelin, and triptorelin. These have to be used for at least 12 months. ○ Oophorectomy (bilateral) *Aromatase inhibitors of interest: anastrozole, exemestane and letrozole.
Comparator	• Ovarian function suppression combined with endocrine therapy using aromatase inhibitors compared to ovarian function suppression combined with tamoxifen • Tamoxifen without ovarian function suppression compared to ovarian function suppression combined with an aromatase inhibitor or ovarian function suppression combined with tamoxifen
Outcomes	**Primary outcomes (critical outcomes)** • Overall survival • Disease-free survival • Quality of life **Secondary outcomes (important outcomes)** • Breast cancer mortality • Adverse events (AEs) ○ treatment-related mortality ○ treatment-related morbidity (specific adverse outcomes of interest only, see appendix M for table with AEs of interest) • Local and/or locoregional recurrence • New contralateral disease • Adherence to or completion of treatment
Study type	• Systematic reviews/meta-analyses of RCTs • RCTs

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and in appendix L – Methods.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

The following methods were specific for this evidence review:

1) The Cochrane systematic review by Bui et al. (2020) was partially used as source of evidence for this evidence review. Six of the included studies in Bui et al. (2020) reporting ovarian function suppression combined with tamoxifen compared to tamoxifen alone met our inclusion criteria (see Table 1 for our inclusion criteria and Table 2 for the included studies in our review).

2) We included data from Yang et al. (2013) which was a conference abstract included by Bui et al. (2020). The authors of the Cochrane systematic review contacted the authors of the publication by Yang et al. (2013) to include data on overall survival and disease-free survival.

3) The committee agreed that some adverse events were more likely to be experienced by people receiving endocrine therapy with or without ovarian function suppression. Adverse events considered important for decision-making were chosen by committee consensus prior to data extraction (see appendix M for the list of adverse events of interest).

4) The risk of bias was assessed using Cochrane's RoB 1 tool by the Bui et al. (2020) Cochrane review. We took their assessment for the studies included by Bui et al. (2020). We used Cochrane's RoB 2 tool to assess the new 5 included studies (ABCSG-12 [Gnant et al. 2008]; ASTRRA [Kim et al. 2020]; HOBOE [Perrone et al. 2019]; TEXT [Pagani et al. 2014]; ZIPP [Nystedt et al. 2000; Baum et al. 2006]) in line with the preferred checklist in Developing NICE guidelines: the manual. Our approach to reach an overall judgement about the risk of bias for each primary study was to:

    a) Low risk of bias: study was judged to be at low risk of bias for all domains or to have some concerns about random sequence generation due to a lack of information provided (as long as allocation concealment was low risk) and/or blinding of participants and personnel. (We agree with Bui et al. (2020) that blinding of participants and personnel is not an issue for the reason they stated in their judgement of the studies: "Performance bias was not considered to be a concern given that there was considerable equipoise at the time at which these studies were conducted such that knowing the treatment allocation was unlikely to affect the behaviour of clinicians and participants").

    b) Some concerns or moderate risk of bias: study was judged to be at unclear risk of bias for allocation concealment or blinding of outcome assessment or selective reporting or incomplete outcome data.

    c) High risk of bias: study was judged to be at high risk of bias for at least one domain or to have multiple domains at unclear risk of bias.

5) We assessed applicability of the includes studies in Bui et al. (2020) based on our review protocol.

6) We included studies with participants receiving concurrent chemotherapy and sensitivity analysis were carried out for overall survival and disease-free survival to determine if the inclusion of such studies affected the overall estimate of effect. This is because chemotherapy can induce menopause which may confound the effectiveness of OFS.

7) Where subgroup analyses were carried out, the null hypothesis that there were no subgroup differences was rejected if the p value for the test for subgroup differences was <0.05.

8) In the protocol for all outcomes without a published minimally important difference (MID) threshold, any statistically significant difference was deemed to be clinically important, and we used the line of no effect as one of the downgrades for imprecision. The quality of the outcome was therefore downgraded once for imprecision if either end of the 95% confidence interval crossed the line of no effect. To be consistent with previous work on this guideline from 2018 we planned to use an event size of 300 events for the second downgrade based on 2018 optimal information size calculations that suggested that at least 300 events were needed to adequately detect an effect. If this information was not readily available, we planned to use sample size instead to ensure that all studies would have the potential to be downgraded twice. Some studies did not report this information for data on hazard ratios and so sample size was used as planned. A minimum sample size of 500 was selected to allow for the possibility of 300 events. As a result, the quality was downgraded a second time if the number of participants for an outcome was less than 500.

9) For adverse events, when meta-analyses included 2 or more studies but some of these studies reported zero events in both arms and only 1 study reported events in either arm, the evidence for that adverse event was downgraded 1 level for inconsistency. This meant that data on that adverse event was considered as only available from 1 study. In these situations, the absolute risk was calculated using only data from the study reporting adverse events in either arm.

10) Some of the included studies were reported by more than one publication. When relevant data was extracted from more than one publication, a footnote was added to the forest plot to note the publication used to extract data.

11) The TEXT and SOFT trials were pooled for the comparison of ovarian function suppression combined with an aromatase inhibitor compared to ovarian function suppression combined with tamoxifen.

12) There was event data reported for time to event outcomes (overall survival: reported by Sun et al. 2021 and HOBOE [Perrone at al. 2019]; breast cancer mortality: reported by SOFT [Francis et al. 2023] and SOFT and TEXT [Pagani et al. 2022]). Log hazard ratio and standard error of log hazard ratio were calculated using number of events and total sample for these outcomes. Footnotes were added to the forest plots to note these calculations. These calculations were done based on the Guideline Methodology Document 3: Meta-Analysis of Event Outcomes.

13) The ABCTCG study reported that 8.4% of participants received goserelin or leuprorelin for at least 2 years, 22.8% had an oophorectomy, and 68.8% had ovarian function suppression by radiation. Overall survival was not reported separately for people with ER positive breast cancer by these types of ovarian function suppression. Therefore, the ABCTCG study was not added to the subgroup analyses by duration of OFS or by method of OFS.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 12 08 2024. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR); Embase (Ovid); Epistemonikos; Medline ALL (Ovid). Full search strategies for each database are provided in Appendix B.

The searches for the cost-effectiveness evidence were run on 15 08 2024. The following databases were searched: Embase (Ovid); Econlit (Ovid); International Health Technology Assessment Database (INAHTA), NHS EED (CRD) and Medline ALL (Ovid). Full search strategies for each database are provided in Appendix B.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. The quality assured (QA) procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Protocol deviations

- Data for a non-English language study (Mitsuyama et al. 2005) was presented in the Cochrane review and we used their data in our analyses, but otherwise non-English language studies were excluded as per the review protocol.
- A conference abstract, Yang et al 2013 was included in this review because the authors of the Cochrane review had obtained data from the authors of Yang et al 2013, but otherwise conference abstracts were excluded as per the review protocol.
- We were planning to extract data from adverse events that were grade 2 and above with the exception of cardiovascular adverse events where only grade 3 and 4 events were extracted (as per committee consensus) and that adverse events would be extracted and reported separately as grade 2 and grade 3 and above where possible. Some of the included studies reported adverse events as 'any grade' without separate data on grade 2 adverse events. Therefore, adverse events reported as 'any grade' were reported as well. Where studies reported more than one type of vasomotor symptoms, we only extracted hot flushes to avoid double counting.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 1024 references (see appendix B for the literature search strategy).

These 1024 references were screened at title and abstract level against the review protocol, with 955 excluded at this level. 10% of references were screened separately by two reviewers with 100% agreement.

The full texts of 51 randomised controlled trials (RCTs) and 18 systematic reviews were ordered for closer inspection. One systematic review and 12 RCTs (published in 20 articles) met the criteria specified in the review protocol (appendix A).

The numbers of studies were as follows for the comparisons of interest:

- Ovarian function suppression combined with tamoxifen compared to tamoxifen alone: 9 studies (ASTRRA; ABCTCG; E-9193, INT-0142; Heo et al. 2017; SOFT; Sun et al. 2021; Yang et al. 2013; ZBCSG Trial B; ZIPP)
- Ovarian function suppression combined with an aromatase inhibitor compared to tamoxifen alone: 2 trials (SOFT and TEXT)
- Ovarian function suppression combined with an aromatase inhibitor compared to ovarian function suppression combined with tamoxifen: 4 trials (ABCSG-12; HOBOE; SOFT and TEXT)

Some studies were 3- (SOFT) or 4-arm studies (ABCSG-12) and some studies provided information for more than 1 comparison of interest (SOFT and TEXT).

For a summary of the systematic review and the 12 RCTs included studies see Table 2 and Table 3.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Cochrane systematic review (for full details of included primary studies, see Bui et al. 2020)

Author (year)	Primary studies from Bui et al. 2020, included in the NICE review	Population covered by systematic review	Intervention*	Comparison	Outcomes	Risk of bias/Applicability of the systematic review
Bui (2020)	• ABCTCG (2007) • E-3193, INT-0142 (Tevaarwerk et al. 2014) • SOFT (Francis et al. 2015) • Yang et al (2013) • Yi et al. (2016) • ZBCSG (Mitsuyama et al. 2005)	**Inclusion criteria:** Types of studies • randomised controlled trials Types of participants • premenopausal women with a histological diagnosis of hormone receptor-positive early breast cancer **Exclusion criteria:** Types of participants • women with metastatic breast cancer Types of interventions	• OFS combined with tamoxifen	• Tamoxifen alone	• Overall survival • Disease-free survival • Contralateral disease • Second malignancy • Adverse events • Compliance with treatment • Quality of life	Low Partially applicable

Author (year)	Primary studies from Bui et al. 2020, included in the NICE review	Population covered by systematic review	Intervention*	Comparison	Outcomes	Risk of bias/Applicability of the systematic review
		• tamoxifen combined with OFS compared to tamoxifen alone				

Abbreviations: OFS: ovarian function suppression. *Note: Bui at al. 2020 also reported results for other comparisons that did not match our review protocol and are therefore not included in the current NICE review.

See appendix D for full evidence tables

Table 3 Randomised controlled trials

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
Studies reporting on the comparison between OFS combined with tamoxifen and tamoxifen alone					
ASTRRA Kim 2020 Baek 2023 Location: South Korea Duration of follow-up: 63 months (median)	Median age: 40 years (24 to 45 years) Total sample size: 1282 % with ER positive breast cancer: 100% Key inclusion criteria: premenopausal women aged ≤45 years with ER positive, stage I - III, primary invasive breast cancer, treated with definitive surgery after completing adjuvant	Tamoxifen 20 mg daily, oral administration for 5 years, combined with OFS induced by goserelin 3.6 mg subcutaneous injection every 28 days for 2 years. Chemotherapy use: all participants had prior neoadjuvant or adjuvant chemotherapy.	Tamoxifen 20 mg daily, oral administration for 5 years. Chemotherapy use: all participants had prior neoadjuvant or adjuvant chemotherapy.	• Overall survival • Disease-free survival • Local and/or locoregional recurrence • New contralateral disease	Objective outcomes: low Directly applicable

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
	or neoadjuvant chemotherapy. WHO performance status of 0,1 or 2 and adequate haematologic, hepatic and renal function. Key exclusion criteria: Other primary malignancies within the past 5 years (except adequately treated in situ carcinoma of the cervix, basal cell carcinoma, or squamous cell skin carcinoma). Cyclophosphamide, methotrexate and fluorouracil chemotherapy regimen Method of determining premenopausal status: Premenopausal status was defined as regular vaginal bleeding history at the time of diagnosis.				
ABCTG 2007 Location: UK, India, Egypt, Malta, New Zealand, Saudi Arabia, Sri Lanka, Iran, Pakistan,	Mean age: 43 years (SD 5.7 years) Total sample size: 2144 % with ER positive BC: 39% Key inclusion criteria: eligible patients were women who were pre or perimenopausal with histologically confirmed early-stage operable (T1-3a N0-1 M0) invasive breast cancer. Premenopausal/perimenopausal	Ovarian ablation or suppression - method of choice was at clinician's discretion, according to centre policy and declared before randomisation. Ovarian ablation or suppression methods: radiation ablation (1600 Gy in 4 fractions), LHRH agonists (goserelin 3.6 mg subcutaneously every 28 days or leuporelin 3.75 mg	Tamoxifen treatment 20 mg daily for at least 5 years, starting within 4 weeks of primary surgery. Chemotherapy use: concurrently given with tamoxifen, if given (79.8% were taking chemotherapy: CMF: 72.4%, anthracycline-containing: 22.2%, other: 5.3%). Use of chemotherapy was at clinician's	• Overall survival	Objective outcomes: low Full study: Partially applicable Data taken from ER

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
Tehran, Singapore Duration of follow-up: 5.9 years (median)	defined as occurrence of the last menstrual period within 12 months preceding breast diagnostic surgery. Key exclusion criteria: previous malignancy (except cervical cancer in situ or basal cell carcinoma); previous systemic therapy for current breast cancer	subcutaneously every 28 days) or surgical ablation. Tamoxifen treatment 20 mg daily for at least 5 years, starting within 4 weeks of primary surgery. Chemotherapy use: concurrently given with tamoxifen, if given (80.3% were taking chemotherapy: CMF: 73.9%, anthracycline-containing: 21.3%, other: 4.8%). Use of chemotherapy was at clinician's discretion and had to be declared before randomisation.	discretion and had to be declared before randomisation.		positive subgroup: Directly applicable (this was used to GRADE the evidence)
E-3193, INT-0142 Tevaarwerk 2014 Location: USA Follow-up time: 9.9 years (median) for recurrence and survival outcomes and 5.86 years	Median age: 45 years, ranging from 26 to 55 years. Total sample size: 34588 % with ER breast cancer: 100% ER and PgR positive. Key inclusion criteria: Eligible patients were premenopausal women with node negative ER positive and /or PgR positive primary invasive breast cancers. Primary tumours ≤3 cm in greatest diameter. Premenopausal status defined as a menstrual period within the past 6 months without prior	Tamoxifen 20 mg daily, oral, combined with OFS of patient / physician choice for 5 years. OFS could consist of LHRH analogue (goserelin 3.6 mg depot every 4 week for 5 years beginning within 4 weeks of assignment; leuprolide acetate 3.75 mg every 4 weeks for 5 years beginning within 4 weeks of random assignment), surgical ablation (done within 12 weeks of random assignment) or radiation ovarian ablation (20 Gy in 10 fractions within 12 weeks	Tamoxifen 20 mg daily, oral for 5 years. No dose reductions were permitted. Other adjuvant systemic therapies were not permitted. Chemotherapy use: chemotherapy was not permitted.	• Overall survival • Disease-free survival • Quality of life • Adherence to or completion of treatment • Adverse events - treatment-related morbidity	Objective outcomes: low Subjective outcomes: moderate Directly applicable

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
(median) for other outcomes.	oophorectomy, or in the case of prior hysterectomy, as age 55 years or younger with one or both ovaries remaining and an oestradiol level in the normal premenopausal range. No prior systemic therapy for breast cancer, aside from ≤ 12 weeks of tamoxifen. Key exclusion criteria: patients with evidence of locally advanced or metastatic disease at diagnosis were ineligible. Premenopausal status defined as a menstrual period within the past 6 months without prior oophorectomy, or in the case of prior hysterectomy, as age 55 years or younger with one or both ovaries remaining and an oestradiol level in the normal premenopausal range.	of random assignment). No dose reductions were permitted. Other adjuvant systemic therapies were not permitted. Chemotherapy use: chemotherapy was not permitted.			
Heo 2017 Location: South Korea Duration of follow-up: patients followed up	Mean age: 44.86 years (35 to 39 years) Total sample size: 64 % with ER positive and/or PgR positive breast cancer: 100% Key inclusion criteria: premenopausal women aged < 50 years with hormone receptor	Tamoxifen and OFS with goserelin for 12 months. Chemotherapy use: no information.	Tamoxifen for 12 months. Chemotherapy use: no information.	• Adverse events - treatment-related morbidity	Subjective outcomes: high Directly applicable

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
for 12 months	positive early invasive breast cancer Key exclusion criteria: age > 50 years, natural menopause, GnRH level ≥40 pg/mL, pregnancy/lactation, uncontrolled heart failure/coronary heart disease in the past 6 months, psychotic disorder, bipolar affective disorder, neurological illness, learning disability, epilepsy, significant medical condition, history of drug/alcohol dependence, personality disorder, brain damage. Method of determining premenopausal status: not reported				
SOFT Francis 2015 Ribi 2016 Francis 2023 Location: Australia, United States of America, Spain, Hungary,	Median age: 43 years Total sample size: 4066 % with ER positive breast cancer: not reported, all participants had hormone receptor positive breast cancer positive (oestrogen or progesterone) Key inclusion criteria: documented premenopausal status, operable breast cancer, tumour that expressed oestrogen or progesterone receptors in at	Tamoxifen 20 mg daily, oral and OFS for 5 years. OFS achieved by either triptorelin 3.75 mg depot administered via intramuscular injection every 28 days or by bilateral oophorectomy or bilateral ovarian irradiation. Patients receiving triptorelin could subsequently choose to undergo oophorectomy or irradiation. Exemestane 25 mg	Tamoxifen 20 mg daily, oral for 5 years. Chemotherapy use: prior chemotherapy was allowed. Subgroup analysis by chemotherapy was reported.	• Overall survival • Disease-free survival • Quality of life • Breast cancer mortality • Local and/or locoregional recurrence	Objective outcomes: low Subjective outcomes: moderate Directly applicable

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
France, Italy, United Kingdom, Germany, Switzerland Duration of follow-up: 8 years median follow-up	least 10% of the cells. Patients had to have undergone either a total mastectomy with or without subsequent radiotherapy or breast-conserving surgery with subsequent radiotherapy. Either axillary dissection or sentinel node biopsy was required. Patients who had not received chemotherapy were randomised within 12 weeks of surgery. Patients who received chemotherapy before randomisation and remained premenopausal were enrolled within 8 months after completing chemotherapy, once perimenopausal oestradiol level was confirmed. Key exclusion criteria: not specified Method of determining premenopausal status: regular menses without exogeneous hormones during prior 6 months and/or oestradiol level in premenopausal range	daily, oral combined with OFS for 5 years. OFS achieved by either triptorelin 3.75 mg depot administered via intramuscular injection every 28 days or by bilateral oophorectomy or bilateral ovarian irradiation. Patients receiving triptorelin could subsequently choose to undergo oophorectomy or irradiation. Chemotherapy use: prior chemotherapy was allowed. Subgroup analysis by chemotherapy was reported.		• New contralateral disease • Adherence to or completion of treatment • Adverse events - treatment-related mortality • Adverse events - treatment-related morbidity	
Sun 2021 Location: China	Mean age: 41.35 years (+/- 5.75 years) Total sample size: 40	Tamoxifen 10 mg twice daily combined with OFS with leuporelin 3.75 mg	Tamoxifen 10 mg twice daily. Chemotherapy use: prior chemotherapy was allowed.	• Overall survival	Objective outcomes: moderate

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
Duration of follow-up: 30 months follow-up	% with ER breast cancer: 100% of ER positive and /or PgR positive breast cancer. Key inclusion criteria: Patients with pathologically confirmed breast cancer who were not menopausal before commencing treatment. Oestrogen receptor positive and /or progesterone receptor positive breast cancer. Patients who had received standard surgery, chemoradiotherapy and other treatments. Key exclusion criteria: Patients who did not complete routine adjuvant therapy. Patients who had a second primary cancer. Presence of serious neurological diseases, mental health condition, severe heart, kidney lung disease or other organ failure disease, coagulation dysfunction. Method of determining premenopausal status: not reported	subcutaneous injection once every 4 weeks for 1 year. Chemotherapy use: prior chemotherapy was allowed.			Directly applicable
Yang 2013 Location: China	Mean age: 42.4 years (OFS), 42.5 (control) Total sample size: 110	Goserelin 3.6 mg every 28 days for 1.5 years combined with tamoxifen 10 mg twice a day for 5 years.	Tamoxifen 10 mg twice a day for 5 years. Chemotherapy use: prior chemotherapy was allowed.	• Overall survival	Objective outcomes: high

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
Duration of follow-up: 72 months	% with ER breast cancer: 100% ER+ and/or PgR+. Key inclusion criteria: provision of informed consent, histologically proven HR+ operable invasive breast cancer, completion of surgery and chemotherapy (if given), women defined as pre- or perimenopausal according to all of the following: aged 50 years or younger, at least one menstrual period during the last months. Key exclusion criteria: metastatic disease, pregnancy or breastfeeding, bilateral oophorectomy, radiation of the ovaries. Method of determining premenopausal status: Premenopausal defined as last menstruation <6 months before trial entry; temporary chemotherapy-induced amenorrhoea allowed if oestradiol level confirmed within 8 months before the final dose of chemotherapy. Key inclusion and exclusion criteria taken from NCT00827307	Chemotherapy use: prior chemotherapy was allowed.		• Disease-free survival	Directly applicable

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
ZBCSG Trial B Mitsuyama 2005 Location: Japan Duration of follow-up: not reported	Age: Not reported Total sample size: 209 % with ER positive breast cancer: 100% Key inclusion criteria: ER positive premenopausal women with breast cancer, lymph node positive or lymph node negative and tumour size >3cm. Key exclusion criteria: none Method of determining premenopausal status: premenopausal defined as women who have a regular menstrual cycle before menopause	Goserelin 3.6 mg depot subcutaneous every 4 weeks for 2 years combined with tamoxifen 10 mg 2 tablets per days or 20 mg 1 tablet per day by mouth, every day for 2 years. Treatment arms received similar co-interventions; no further information reported. Chemotherapy use: no information.	Tamoxifen 10 mg 2 tablets per days or 20 mg 1 tablet per day by mouth, every day for 2 years. Treatment arms received similar co-interventions; no further information reported. Chemotherapy use: no information.	• Adverse events - treatment-related morbidity	Subjective outcomes: high Directly applicable
ZIPP (multicentre) Baum 2006 Hackshaw 2009 Location: Italy, Sweden, UK Duration of follow-up: median	Median age: 44 years (21 to 56 years) Total sample size: 2710 % ER positive: 50% in tamoxifen combined with OFS group, 53% in tamoxifen group Key inclusion criteria: Premenopausal aged women aged 50 years or under with operable stage 1 or 2 breast cancer, regardless of ER status. Invasive breast cancer confined to one breast. No evidence of	Tamoxifen combined with OFS. Tamoxifen 20 mg or 40 mg daily, oral, and OFS. OFS using goserelin 3.6 mg subcutaneous injection into the abdominal wall every 28 days. Randomised therapy was continued for 2 years. Local treatment (surgery with or without radiotherapy) and adjuvant chemotherapy (where appropriate) were planned according to local treatment policies prior to randomisation. Peri-operative	Tamoxifen 20 mg or 40 mg daily, oral. Randomised therapy was continued for 2 years. Local treatment (surgery with or without radiotherapy) and adjuvant chemotherapy (where appropriate) were planned according to local treatment policies prior to randomisation. Peri-operative cyclophosphamide or six cycles of cyclophosphamide/methotrexate /5-fluorouracil chemotherapy	• Overall survival • Disease-free survival	Objective outcomes: high Full study: Partially applicable Data taken from ER positive subgroup: Directly

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
follow-up 5.5 years	distant metastases. Normal liver and renal function and full blood counts. Key exclusion criteria: Hormonal therapy within the 6 weeks prior to joining the trial. Unsuitable for surgery (or radiotherapy, if relevant). Severely limited life expectancy due to intercurrent illness. Previous treatment for other malignancies (with the exception of basal or squamous cell carcinoma of the skin, or adequately biopsied in situ carcinoma of the cervix). Primary carcinoma fixed to underlying muscle of chest wall, or was ulcerated, had skin infiltration or presence of axillary nodes that demonstrated deep fixity.	cyclophosphamide or six cycles of cyclophosphamide/methotrexate /5-fluorouracil chemotherapy was recommended in the protocol but some centres used a standard 5-fluoruocil/epirubicin/cyclophosphamide regimen). Chemotherapy use: prior chemotherapy was allowed.	was recommended in the protocol but some centres used a standard 5-fluoruocil/epirubicin/cyclophosphamide regimen). Chemotherapy use: prior chemotherapy was allowed.		applicable (this was used to GRADE the evidence)
Studies reporting on the comparison between OFS combined with an aromatase inhibitor and tamoxifen alone					
SOFT Francis 2015 Francis 2023	See above for details on participants.	See above for details on interventions.	See above for details on comparators.	See above for details on outcomes.	See above for details on risk of bias and applicability.
SOFT and TEXT Francis 2018 Location: Australia,	Median age: 43 years (39 to 47 years) (TEXT and SOFT combined) Total sample size: 4717 (TEXT and SOFT combined)	Tamoxifen 20 mg daily, oral combined with OFS, for 5 years. OFS achieved with triptorelin 3.75 mg depot intramuscular injection every 28 days. Bilateral	Exemestane 25 mg daily, oral, combined with OFS, for 5 years. OFS achieved with triptorelin 3.75 mg depot intramuscular injection every 28 days. Bilateral	• Overall survival • Disease-free survival	Objective outcomes: low

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
Belgium, Canada, Egypt, Germany, Hungary, India, Italy, Peru, Slovenia, South Africa, Sweden, Switzerland, UK, USA Duration of follow-up: 68 months median follow-up	% with ER positive breast cancer: 97% (88% with ER and PgR positive breast cancer; 9% with ER positive breast and PgR negative breast cancer, TEXT and SOFT combined) Key inclusion criteria: Documented premenopausal status. Operable breast cancer confined to the breast and ipsilateral axilla, with the exception of internal-mammary-node involvement detected by means of sentinel node biopsy. Tumour that expressed oestrogen or progesterone receptors in at least 10% of the cells. Total mastectomy with subsequent optional radiotherapy, or breast-conserving surgery with subsequent radiotherapy. Key exclusion criteria: Patients in the TEXT trial were not allowed to receive adjuvant oral endocrine therapy before randomisation.	oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin. Chemotherapy use: it was optional. If administered, chemotherapy was started concomitantly with triptorelin; oral endocrine therapy was started 6 to 8 weeks after the initiation of triptorelin.	oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin. Chemotherapy use: it was optional. If administered, chemotherapy was started concomitantly with triptorelin; oral endocrine therapy was started 6 to 8 weeks after the initiation of triptorelin.	• Local and/or locoregional recurrence • New contralateral disease • Adherence to or completion of treatment • Adverse events - treatment-related mortality • Adverse events - treatment-related morbidity	Subjective outcomes: high Directly applicable
Studies reporting on the comparison between OFS combined with an aromatase inhibitor and OFS combined with tamoxifen					
ABCSG-12 Gnant 2008 Gnant 2011	Median age was 46.6 years in tamoxifen + OFS arm, 43.8 years in tamoxifen + OFS + zoledronic acid arm, 45.7 years in	Tamoxifen and OFS: 3 years of goserelin (3.6 mg daily subcutaneously every 28 days)	Anastrozole and OFS: 3 years of goserelin (3.6 mg daily subcutaneously every 28 days)	• Overall survival	Objective outcomes: low

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
Gnant 2015 Location: Austria Follow-up: 60 months (median)	anastrozole + OFS arm, 44.7 years in anastrozole + OFS + zoledronic acid arm. Total sample size: 40195 % with ER positive breast cancer: 100% with ER and/or PgR. Key inclusion criteria: Premenopausal women ≥ 19 years of age who had received surgery for stage I/II ER positive or PgR positive (or both) breast cancer; Karnofsky Index of 70 or greater; fewer than 10 positive lymph nodes; scheduled to receive goserelin for 3 years. Key exclusion criteria: T1a (except yT1a), T4d or yT4 breast cancer; history of other tumours /cytotoxic chemotherapy (preoperative chemotherapy was allowed); preoperative radiotherapy; pregnancy/lactation; oral contraception; serum creatinine concentration ≥265 µmol/L; serum calcium concentration of less < 2 mmol/L or > than 3 mmol/L; bisphosphonate/long-term anti-convulsive therapy within 1 year of study entry; current/previous	combined with tamoxifen (20 mg daily orally). Tamoxifen and OFS and zoledronic acid: 3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with tamoxifen (20 mg daily orally) plus zoledronic acid (4 mg intravenously every 6 months) Chemotherapy use: a history of preoperative chemotherapy was allowed; otherwise cytotoxic chemotherapy was an exclusion criterion.	combined with anastrozole (1 mg/day orally). Anastrazole and OFS and zoledronic: 3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with anastrozole (1 mg/day orally) plus zoledronic acid (4 mg intravenously every 6 months). Chemotherapy use: a history of preoperative chemotherapy was allowed; otherwise cytotoxic chemotherapy was an exclusion criterion.	• Disease-free survival • Breast cancer mortality • Local and/or locoregional recurrence • New contralateral disease • Adherence to or completion of treatment • Adverse events - treatment-related morbidity	Subjective outcomes: high Partially applicable

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
	bone disease; long-term corticosteroid therapy; previous adjuvant chemotherapy; osteomalacia/osteogenesis imperfecta/osteoporosis. No information about preoperative chemotherapy in the baseline characteristics. Patients' premenopausal status was defined by a clinically estimated regular menstrual cycle or a last menstrual cycle occurring not more than 1 year before study entry. In women with indeterminate menstrual status (for example, after hysterectomy), serum concentrations of follicle-stimulating hormone and luteinising hormone were used to establish premenopausal status.				
HOBOE Perrone 2019 Location: Italy Duration of follow-up: 64 months	Median age: 45 years (41 to 48 years) Total sample size: 710 (Tamoxifen combined with OFS and Letrozole combined with OFS arms) % with ER positive breast cancer: 100% Key inclusion criteria: Premenopausal women aged ≥18	Tamoxifen 20 mg/ day orally for 5 years combined with OFS (intramuscular triptorelin 3.75 mg at the start of treatment and then every 4 weeks) for 5 years or up to 55 years of age. Radiotherapy on the residual breast, lymph node stations and thoracic wall was allowed if indicated by international	Letrozole 2.5 mg/day for 5 years combined with OFS (intramuscular triptorelin 3.75 mg at the start of treatment and then every 4 weeks) for 5 years or up to 55 years of age. Radiotherapy on the residual breast, lymph node stations and thoracic wall was allowed if indicated by international	• Overall survival • Disease-free survival • Local and/or locoregional recurrence	Objective outcomes: low Subjective outcomes: high

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
median follow-up	years with histologically confirmed ER and/or PgR positive breast cancer completely removed by surgery. Any pathologic tumour size and axillary nodal status. No evidence of recurrence. Patients who had received neoadjuvant or adjuvant chemotherapy and/or locoregional radiotherapy could be included. Key exclusion criteria: Previous malignant neoplasia (excluding adequately treated basal or spinocellular cutaneous carcinoma and in situ carcinoma of the uterine cervix). Previous treatment with tamoxifen or aromatase inhibitors. Pregnancy/lactation. Serum creatinine level >1.25 times the maximum normal value. AST and/or ALT >3 times the normal value. Clinical/radiological evidence of active bone fractures. Presence of concomitant disease contraindicating study drugs. Current or planned invasive dental therapy. Method of determining premenopausal status: last	standards, before or during the hormonal treatment. Trastuzumab was allowed in patients with HER2 positive breast cancer. Randomisation was performed after completion of surgery and adjuvant chemotherapy. Radiotherapy and trastuzumab could overlap with hormonal treatment. Chemotherapy use: previous neoadjuvant and/or adjuvant chemotherapy was allowed.	standards, before or during the hormonal treatment. Trastuzumab was allowed in patients with HER2 positive breast cancer. Randomisation was performed after completion of surgery and adjuvant chemotherapy. Radiotherapy and trastuzumab could overlap with hormonal treatment. Chemotherapy use: previous neoadjuvant and/or adjuvant chemotherapy was allowed.	• New contralateral disease • Adherence to or completion of treatment • Adverse events - treatment-related morbidity	Directly applicable

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias* Applicability
	menstrual cycle within 12 months prior to randomisation. Levels of FSH, LH and oestradiol were not used to define premenopausal status.				
SOFT Francis 2015 Francis 2023	See above for details on participants.	See above for details on interventions.	See above for details on comparators.	See above for details on outcomes.	See above for details on risk of bias and applicability.
SOFT and TEXT Pagani 2014 Francis 2018 Pagani 2022	See above for details on participants.	See above for details on interventions.	See above for details on comparators.	See above for details on outcomes.	See above for details on risk of bias and applicability.

* Risk of bias by type of outcome (objective outcomes: overall survival, disease-free survival, breast cancer mortality, treatment-related mortality, local and/or locoregional recurrence, new contralateral disease; subjective outcomes: quality of life, treatment-related morbidity, adherence or completion of treatment).

Abbreviations: aspartate aminotransferase (AST), alanine aminotransferase (ALT), breast cancer (BC), cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), oestrogen receptor (ER), follicle stimulating hormone (FSH), gonadotropin hormone-releasing hormone (GnRH), human epidermal growth factor receptor 2 (HER2), hormone receptor (HR), LH (luteinising-hormone), luteinising-hormone-releasing hormone (LHRH), metastasis (M), lymph node (N), ovarian function suppression (OFS), progesterone receptor (PgR), tumour size (T), World Health Organization (WHO).

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Interpreting the effectiveness evidence

In the absence of published minimally important differences (MIDs) clinical decision thresholds were agreed with the committee and used to interpret the evidence. The line of no effect (in this case represented by 1.0 for dichotomous outcomes and 0 for continuous outcomes) was used as a clinical decision threshold.

The following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables:

For outcomes without a published MID or where the clinical decision threshold is set as the line of no effect, the results are divided into 2 groups as follows:

- The evidence showed that there is an effect if the 95% CI does not cross the line of no effect. (Where this an effect, we will state the direction of the effect.)
- It was not possible from the evidence to differentiate between comparators if the 95% CI crosses the line of no effect (shortened to 'could not differentiate').
- .

Where published MIDs were available the following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables. The results were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect. (Where this an effect, we will state the direction of the effect.)
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.

- In all other cases, we state that it was not possible from the evidence to differentiate between the comparators (shortened to ‘could not differentiate’).

Ovarian function suppression combined with tamoxifen compared to tamoxifen alone

Overall survival

Table 4 Summary GRADE table for overall survival

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Overall survival - 2.5 to 6 years follow-up	68 per 1,000 [a]	52 per 1,000 (42 to 63) [a]	HR 0.76 (0.62 to 0.92)	5521 (7 RCTs)	High	Effect favours OFS combined with tamoxifen
Overall survival – 2.5 to 6 years follow-up sensitivity analysis without study with concurrent chemotherapy (ABCTCG study)	68 per 1,000 [b]	52 per 1,000 (42 to 63) [b]	HR 0.72 (0.57 to 0.92)	4683 (6 RCTs)	High	Effect favours OFS combined with tamoxifen
Overall survival - 8 to 12 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)	124 per 1,000 [c]	97 per 1,000 (74 to 125) [c]	HR 0.78 (0.62 to 0.98)	3315 (2 RCTs)	High	Effect favours OFS combined with tamoxifen
Overall survival - 12 years follow-up - subgroup analysis by HER2 status - HER2 negative	117 per 1,000	101 per 1,000 (76 to 133)	HR 0.86 (0.65 to 1.14)	1728 (1 RCT)	Low	Could not differentiate
Overall survival - 12 years follow-up - subgroup analysis by HER2 status - HER2 positive	169 per 1,000	61 per 1,000 (27 to 134)	HR 0.36 (0.16 to 0.79)	237 (1 RCT)	Low	Effect favours OFS combined with tamoxifen

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). a. Absolute effects estimated from 5 RCTs as 2 RCTs (ABCTCG, Yang 2013) did not report number of events. b. Absolute effects

estimated from 5 RCTs as 1 RCT (Yang 2013) did not report number of events. c. Absolute effects estimated from 1 RCT as 1 RCT (ASTRRA) did not report number of events. ** Hazard ratios of less than 1 mean fewer deaths. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; HR: hazard ratio; OFS: ovarian function suppression.

Disease-free survival

Table 5 Summary GRADE table for disease-free survival

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Disease-free survival - 5 to 6 years follow-up	144 per 1,000 [a]	114 per 1,000 (95 to 135) [a]	HR 0.79 (0.66 to 0.94)	3743 (4 RCTs)	High	Effect favours OFS combined with tamoxifen
Disease-free survival - 5 years follow-up - subgroup analysis by HER2 status - HER2 negative	145 per 1,000	122 per 1,000 (99 to 151)	HR 0.84 (0.68 to 1.04)	2500 (2 RCTs)	Moderate	Could not differentiate
Disease-free survival - 5 years follow-up - subgroup analysis by HER2 status - HER2 positive	187 per 1,000	82 per 1,000 (49 to 142)	HR 0.44 (0.26 to 0.76)	412 (2 RCTs)	Moderate	Effect favours OFS combined with tamoxifen
Disease-free survival - 8 to 12 years follow-up (all luteinising -hormone releasing hormone agonists)	241 per 1,000 [b]	193 per 1,000 (171 to 217) [b]	HR 0.80 (0.71 to 0.90)	5076 (3 RCTs)	High	Effect favours OFS combined with tamoxifen

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). a. Absolute effects estimated from 3 RCTs as 1 RCT (Yang 2013) did not report number of events. b. Absolute effects estimated

from 2 RCTs as 1 RCT (ZIPP Multicentre) did not report number of events. ** Hazard ratios of less than 1 mean fewer deaths or recurrences. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; HR: hazard ratio; OFS: ovarian function suppression.

Breast cancer mortality

Table 6 Summary GRADE table for Breast cancer mortality

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Breast cancer mortality - 12 years follow-up	108 per 1,000	90 per 1,000 (68 to 119)	HR 0.83 (0.63 to 1.10)	2033 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; HR: hazard ratio; OFS: ovarian function suppression.

Local and/or locoregional recurrence

Table 7 Summary GRADE table for Local and/or locoregional recurrence

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Local and/or locoregional recurrence - 5 years follow-up	33 per 1,000	18 per 1,000 (12 to 28)	RR 0.55 (0.35 to 0.85)	3315 (2 RCTs)	High	Effect favours OFS combined with tamoxifen
Local and/or locoregional recurrence - 8 to 12 years follow-up	59 per 1,000	41 per 1,000 (30 to 56)	RR 0.69 (0.51 to 0.94)	3315 (2 RCTs)	High	Effect favours OFS combined with tamoxifen

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

New contralateral disease

Table 8 Summary GRADE table for new contralateral disease

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
New contralateral disease – 5 years follow-up	12 per 1,000	10 per 1,000 (5 to 19)	RR 0.81 (0.42 to 1.55)	3315 (2 RCTs)	Moderate	Could not differentiate
New contralateral disease – 8 to 12 years follow-up	22 per 1,000	22 per 1,000 (8 to 58)	RR 0.98 (0.37 to 2.62)	3315 (2 RCTs)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Adherence to or completion of treatment

Table 9 Summary GRADE table for adherence to or completion of treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Adherence to or completion of treatment (treatment completed at 5 years)	414 per 1,000	481 per 1,000 (439 to 526)	RR 1.16 (1.06 to 1.27)	2370 (2 RCTs)	High	Effect favours OFS combined with tamoxifen

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Quality of life

Table 10 Summary GRADE table for quality of life

Outcomes	Risk with OFS combined with tamoxifen	№ of participants (studies)	Certainty of the evidence (GRADE)*	Interpretation of effect
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - FACT-B (MID +/-8 points)	MD 3.42 higher (2.32 lower to 9.16 higher)	116 (1 RCT)	Low	Could not differentiate

Outcomes	Risk with OFS combined with tamoxifen	№ of participants (studies)	Certainty of the evidence (GRADE)*	Interpretation of effect
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - FACT-G (MID +/-7 points)	MD 1.5 lower (5.32 lower to 2.32 higher)	184 (1 RCT)	Moderate	No meaningful difference
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - Breast subscale (MID +/-3 points)	MD 2.44 higher (0.21 higher to 4.67 higher)	119 (1 RCT)	Low	Effect favours OFS combined with tamoxifen but effect is less than the defined MID
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - Menopausal symptoms	MD 3.25 lower (6.19 lower to 0.31 lower)	174 (1 RCT)	Low	Effect favours tamoxifen alone
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - Sexual function	MD 1.8 lower (3.45 lower to 0.15 lower)	141 (1 RCT)	Low	Effect favours tamoxifen alone
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Physical wellbeing	MD 2 higher (1.5 lower to 5.5 higher)	1722 (1 RCT)	Low	Could not differentiate
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Mood	MD 2 higher (1 lower to 5 higher)	1722 (1 RCT)	Low	Could not differentiate
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Coping effort	MD 2 lower (5.5 lower to 1.5 higher)	1722 (1 RCT)	Low	Could not differentiate

Outcomes	Risk with OFS combined with tamoxifen	№ of participants (studies)	Certainty of the evidence (GRADE)*	Interpretation of effect
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Treatment burden	MD 1 lower (4.5 lower to 2.5 higher)	1722 (1 RCT)	Low	Could not differentiate
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Health perception	MD 1 higher (1.5 lower to 3.5 higher)	1722 (1 RCT)	Low	Could not differentiate

*See full GRADE tables (appendix F) for reasons for downgrading the evidence. FACT-B: Functional Assessment of Cancer Therapy – Breast questionnaire; FACT-G: Functional Assessment of Cancer Therapy – General questionnaire; CI: confidence interval; MD: mean difference; MID: minimally important difference; OFS: ovarian function suppression.

Treatment-related mortality

Table 11 Summary GRADE table for treatment-related mortality

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Treatment-related mortality - cardiac ischaemia or infarction (grade 5)	Not estimable**	Not estimable**	RR 0.33 (0.01 to 8.18)	2011 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Absolute effects could not be estimated because there were 0 events in one of the arms. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Adverse events

Table 12 Summary GRADE table for genitourinary adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Vaginal dryness - any grade	418 per 1,000	498 per 1,000 (452 to 548)	RR 1.19 (1.08 to 1.31)	2011 (1 RCT)	High	Effect favours tamoxifen alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Vaginal dryness - grade 3	Not estimable**	Not estimable**	RR 2.95 (0.12 to 71.88)	345 (1 RCT)	Very low	Could not differentiate
Incontinence - any grade	161 per 1,000	184 per 1,000 (151 to 222)	RR 1.14 (0.94 to 1.38)	2011 (1 RCT)	Low	Could not differentiate
Incontinence - grades 3 to 4	6 per 1,000	5 per 1,000 (2 to 16)	RR 0.83 (0.26 to 2.72)	2011 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Absolute effects could not be estimated because there were 0 events in one of the arms. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 13 Summary GRADE table for menopausal adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Vasomotor symptoms (any grade) - RE model	733 per 1,000	1000 per 1,000 (249 to 1,000)	RR 3.20 (0.34 to 30.09)	2123 (2 RCTs)	Very low	Could not differentiate
Vasomotor symptoms (hot flushes) - grade 3 - RE model	71 per 1,000	159 per 1,000 (84 to 300)	RR 2.23 (1.18 to 4.21)	2356 (2 RCTs)	Low	Effect favours tamoxifen alone
Sleep disturbances or insomnia - any grade	463 per 1,000	574 per 1,000 (523 to 625)	RR 1.24 (1.13 to 1.35)	2011 (1 RCT)	Moderate	Effect favours tamoxifen alone
Insomnia - grades 3 to 4	26 per 1,000	39 per 1,000 (25 to 61)	RR 1.48 (0.95 to 2.30)	2356 (2 RCTs)	Low	Could not differentiate
Fatigue - any grade	599 per 1,000	629 per 1,000 (587 to 671)	RR 1.05 (0.98 to 1.12)	2011 (1 RCT)	Moderate	Could not differentiate
Fatigue - grades 3 to 4	32 per 1,000	36 per 1,000 (23 to 57)	RR 1.13 (0.71 to 1.80)	2011 (1 RCT)	Low	Could not differentiate
Weight gain - any grade	54 per 1,000	100 per 1,000 (21 to 479)	RR 1.84 (0.38 to 8.82)	112 (1 RCT)	Very low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Weight gain - grades 3 to 4	23 per 1,000	34 per 1,000 (10 to 120)	RR 1.47 (0.42 to 5.13)	345 (1 RCT)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 14 Summary GRADE table for glucose intolerance

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Glucose intolerance any grade	18 per 1,000	35 per 1,000 (20 to 61)	RR 1.95 (1.11 to 3.41)	2011 (1 RCT)	Moderate	Effect favours tamoxifen alone
Glucose intolerance - grades 3 to 4	3 per 1,000	11 per 1,000 (4 to 36)	RR 4.42 (1.39 to 14.07)	2356 (2 RCTs)	High	Effect favours tamoxifen alone

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 15 Summary GRADE table for neurocognitive adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Depression - any grade	466 per 1,000	517 per 1,000 (476 to 569)	RR 1.11 (1.02 to 1.22)	2011 (1 RCT)	Moderate	Effect favours tamoxifen alone
Depression - grades 3 to 4	38 per 1,000	44 per 1,000 (29 to 67)	RR 1.16 (0.76 to 1.77)	2011 (1 RCT)	Low	Could not differentiate
Anxiety - moderate to severe	438 per 1,000	407 per 1,000 (228 to 722)	RR 0.93 (0.52 to 1.65)	64 (1 RCT)	Very low	Could not differentiate
Depression and/or anxiety - grade 4	23 per 1,000	23 per 1,000 (6 to 91)	RR 0.98 (0.25 to 3.87)	345 (1 RCT)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 16 Summary GRADE table for psychosexual adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Decreased libido or dyspareunia- any grade	661 per 1,000	734 per 1,000 (694 to 780)	RR 1.11 (1.05 to 1.18)	2011 (1 RCT)	Moderate	Effect favours tamoxifen alone
Changes in libido or dyspareunia- grades 3 to 4	12 per 1,000	19 per 1,000 (10 to 37)	RR 1.62 (0.85 to 3.10)	2356 (2 RCTs)	Moderate	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 17 Summary GRADE table for musculoskeletal adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Fractures - any grade	49 per 1,000	54 per 1,000 (37 to 78)	RR 1.10 (0.76 to 1.61)	2011 (1 RCT)	Low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Fractures - grades 3 to 4	8 per 1,000	8 per 1,000 (3 to 21)	RR 1.00 (0.38 to 2.66)	2011 (1 RCT)	Low	Could not differentiate
Osteoporosis - any grade	123 per 1,000	200 per 1,000 (163 to 245)	RR 1.62 (1.32 to 1.99)	2011 (1 RCT)	Moderate	Effect favours tamoxifen alone
Osteoporosis - grades 3 to 4	1 per 1,000	3 per 1,000 (0 to 29)	RR 3.00 (0.31 to 28.82)	2011 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 18 Summary GRADE table for cardiovascular adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Thrombosis or embolism grades 3 to 4	17 per 1,000	17 per 1,000 (9 to 33)	RR 1.00 (0.51 to 1.95)	2011 (1 RCT)	Low	Could not differentiate
Cardiac ischaemia or infarction - grades 3 to 4	3 per 1,000	1 per 1,000 (0 to 10)	RR 0.33 (0.03 to 3.20)	2011 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 19 Summary GRADE table for other cancers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with tamoxifen				
Other cancers	38 per 1,000	36 per 1,000 (23 to 56)	RR 0.93 (0.59 to 1.45)	2032 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Ovarian function suppression combined with an aromatase inhibitor compared to tamoxifen alone

Overall survival

Table 20 Summary GRADE table for overall survival

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Overall survival - 5 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)	58 per 1,000	56 per 1,000 (39 to 81)	HR 0.97 (0.68 to 1.39)	2032 (1 RCT)	Low	Could not differentiate
Overall survival - 12 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)	124 per 1,000	99 per 1,000 (77 to 129)	HR 0.80 (0.62 to 1.04)	2032 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Hazard ratios of less than 1 mean fewer deaths. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; HR: risk ratio.

Disease-free survival

Table 21 Summary GRADE table for disease-free survival

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Disease-free survival - 5 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)	157 per 1,000	107 per 1,000 (83 to 137)	HR 0.68 (0.53 to 0.87)	2032 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor
Disease-free survival - 12 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)	224 per 1,000	155 per 1,000 (128 to 186)	HR 0.69 (0.57 to 0.83)	2032 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ** Hazard ratios of less than 1 mean fewer deaths or recurrences. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; HR: risk ratio.

Breast cancer mortality

Table 22 Summary GRADE table for breast cancer mortality

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Breast cancer mortality - 12 years follow-up	108 per 1,000	83 per 1,000 (63 to 110)	HR 0.77 (0.58 to 1.02)	2032 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; HR: risk ratio.

Local and/or locoregional recurrence

Table 23 Summary GRADE table for local and/or locoregional recurrence

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Local and/or locoregional recurrence - 12 years follow-up	65 per 1,000	36 per 1,000 (24 to 53)	RR 0.55 (0.37 to 0.81)	2032 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

New contralateral disease

Table 24 Summary GRADE table for new contralateral disease

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
New contralateral disease - 12 years follow-up	31 per 1,000	16 per 1,000 (9 to 29)	RR 0.50 (0.28 to 0.91)	2032 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Adherence to or completion of treatment

Table 25 Summary GRADE table for adherence to or completion of treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Adherence to or completion of treatment (treatment completed at 8 years)	757 per 1,000	788 per 1,000 (750 to 826)	RR 1.04 (0.99 to 1.09)	2032 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Quality of life

No evidence identified for this outcome

Treatment-related mortality

Table 26 Summary GRADE table for treatment-related mortality

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Treatment-related mortality	Not estimable**	Not estimable**	RR 0.14 (0.01 to 3.55)	3322 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Absolute effects could not be estimated because there were 0 events in one of the arms. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Adverse events

Table 27 Summary GRADE table for genitourinary adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Vaginal dryness - any grade	424 per 1,000	538 per 1,000 (496 to 585)	RR 1.27 (1.17 to 1.38)	3322 (1 RCT)	Moderate	Effect favours tamoxifen alone
Incontinence - any grade	165 per 1,000	137 per 1,000 (116 to 162)	RR 0.83 (0.70 to 0.98)	3322 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor
Incontinence - grades 3 to 4	6 per 1,000	4 per 1,000 (1 to 11)	RR 0.65 (0.23 to 1.82)	3322 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 28 Summary GRADE table for menopausal adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Vasomotor symptoms (hot flushes)- any grade	804 per 1,000	925 per 1,000 (892 to 957)	RR 1.15 (1.11 to 1.19)	3322 (1 RCT)	Moderate	Effect favours tamoxifen alone
Vasomotor symptoms (hot flushes) - grades 3 to 4	78 per 1,000	101 per 1,000 (79 to 129)	RR 1.30 (1.02 to 1.66)	3322 (1 RCT)	Moderate	Effect favours tamoxifen alone
Sleep disturbances - any grade	468 per 1,000	594 per 1,000 (552 to 641)	RR 1.27 (1.18 to 1.37)	3322 (1 RCT)	Moderate	Effect favours tamoxifen alone
Insomnia - grades 3 to 4	30 per 1,000	39 per 1,000 (26 to 58)	RR 1.29 (0.86 to 1.93)	3322 (1 RCT)	Low	Could not differentiate
Fatigue - any grade	609 per 1,000	627 per 1,000 (591 to 664)	RR 1.03 (0.97 to 1.09)	3322 (1 RCT)	Low	Could not differentiate
Fatigue - grades 3 to 4	34 per 1,000	32 per 1,000 (22 to 48)	RR 0.96 (0.64 to 1.43)	3322 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 29 Summary GRADE table for glucose intolerance

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Glucose intolerance - any grade	18 per 1,000	27 per 1,000 (16 to 46)	RR 1.52 (0.90 to 2.55)	3322 (1 RCT)	Low	Could not differentiate
Glucose intolerance - grades 3 to 4	4 per 1,000	6 per 1,000 (2 to 19)	RR 1.63 (0.54 to 4.89)	3322 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 30 Summary GRADE table for neurocognitive adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Depression - any grade	474 per 1,000	516 per 1,000 (478 to 559)	RR 1.09 (1.01 to 1.18)	3322 (1 RCT)	Moderate	Effect favours tamoxifen alone
Depression - grades 3 to 4	41 per 1,000	41 per 1,000 (29 to 59)	RR 1.01 (0.70 to 1.44)	3322 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 31 Summary GRADE table for psychosexual adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Decreased libido - any grade	432 per 1,000	458 per 1,000 (419 to 497)	RR 1.06 (0.97 to 1.15)	3322 (1 RCT)	Low	Could not differentiate
Dyspareunia - any grade	241 per 1,000	315 per 1,000 (279 to 359)	RR 1.31 (1.16 to 1.49)	3322 (1 RCT)	Moderate	Effect favours tamoxifen alone
Dyspareunia - grades 3 to 4	16 per 1,000	24 per 1,000 (14 to 42)	RR 1.52 (0.88 to 2.63)	3322 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 32 Summary GRADE table for musculoskeletal adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Fractures - any grade	53 per 1,000	77 per 1,000 (57 to 104)	RR 1.46 (1.09 to 1.97)	3322 (1 RCT)	Moderate	Effect favours tamoxifen alone
Fractures - grades 3 to 4	8 per 1,000	16 per 1,000 (7 to 34)	RR 2.01 (0.94 to 4.29)	3322 (1 RCT)	Low	Could not differentiate
Osteoporosis - any grade	137 per 1,000	422 per 1,000 (360 to 496)	RR 3.07 (2.62 to 3.61)	3322 (1 RCT)	Moderate	Effect favours tamoxifen alone
Osteoporosis - grades 3 to 4	1 per 1,000	4 per 1,000 (1 to 34)	RR 4.34 (0.56 to 33.84)	3322 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 33 Summary GRADE table for cardiovascular adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Thrombosis or embolism - grades 3 to 4	17 per 1,000	9 per 1,000 (5 to 16)	RR 0.51 (0.27 to 0.97)	3322 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor
Cardiac ischaemia or infarction - grades 3 to 4	4 per 1,000	3 per 1,000 (1 to 10)	RR 0.76 (0.22 to 2.59)	3322 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 34 Summary GRADE table for other cancers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with OFS combined with an AI				
Other cancers	38 per 1,000	33 per 1,000 (21 to 51)	RR 0.85 (0.54 to 1.34)	2032 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Ovarian function suppression combined with an aromatase inhibitor compared to ovarian function suppression combined with tamoxifen

Overall survival

Table 35 Summary GRADE table for overall survival

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Overall survival - 5 years follow-up (all with method of OFS: luteinising-hormone releasing hormone agonists)	38 per 1,000	44 per 1,000 (29 to 69)	HR 1.16 (0.75 to 1.81)	7203 (3 RCTs)	Very low	Could not differentiate
Overall survival - 8 to 12 years follow-up (all with method of OFS: luteinising-hormone releasing hormone agonists)	86 per 1,000	102 per 1,000 (59 to 176)	HR 1.19 (0.69 to 2.05)	6493 (2 RCTs)	Very low	Could not differentiate
Overall survival - 8 to 12 years follow-up – sensitivity analysis without study with concurrent chemotherapy (TEXT study)	65 per 1,000	81 per 1,000 (51 to 128)	HR 1.24 (0.78 to 1.97)	4886 (2 RCTs)	Very low	Could not differentiate
Overall survival - 8 to 12 years follow-up – subgroup analysis by duration of OFS: less than 5 years	37 per 1,000	60 per 1,000 (39 to 94)	HR 1.63 (1.05 to 2.53)	1803 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Overall survival - 8 to 12 years follow-up – subgroup analysis by duration of OFS: 5 years	105 per 1,000	98 per 1,000 (82 to 117)	HR 0.93 (0.78 to 1.11)	4690 (1 RCT)	Low	Could not differentiate
Overall survival - 8 years follow-up - subgroup analysis by HER2 status - HER2 negative	70 per 1,000	60 per 1,000 (48 to 77)	HR 0.86 (0.68 to 1.09)	4035 (1 RCT)	Low	Effect favours OFS combined with an aromatase inhibitor
Overall survival - 8 years follow-up - subgroup analysis by HER2 status - HER2 positive	57 per 1,000	109 per 1,000 (60 to 197)	HR 1.91 (1.05 to 3.47)	578 (1 RCT)	Moderate	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ** Hazard ratios of less than 1 mean fewer deaths. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; HR: risk ratio.

Disease-free survival

Table 36 Summary GRADE table for disease-free survival

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Disease-free survival - 5 years follow-up (all with method of OFS: luteinising-hormone releasing hormone agonists)	124 per 1,000	102 per 1,000 (78 to 134)	HR 0.82 (0.63 to 1.08)	7203 (3 RCTs)	Very low	Could not differentiate
Disease-free survival - 5 years follow-up – sensitivity analysis without study with concurrent chemotherapy (TEXT study)	113 per 1,000	95 per 1,000 (72 to 124)	HR 0.84 (0.64 to 1.10)	5596 (3 RCTs)	Low	Could not differentiate
Disease-free survival - 5 years follow-up – subgroup analysis by duration of OFS: less than 5 years (RE model to match main analysis)	99 per 1,000	107 per 1,000 (80 to 143)	HR 1.08 (0.81 to 1.44)	1803 (1 RCT)	Low	Could not differentiate
Disease-free survival - 5 years follow-up – subgroup analysis by duration of OFS: 5 years (RE model to match main analysis)	132 per 1,000	95 per 1,000 (83 to143)	HR 0.72 (0.61 to 0.84)	5400 (2 RCTs)	High	Effect favours OFS combined with an aromatase inhibitor
Disease-free survival - 5 years follow-up - subgroup analysis by HER2 status - HER2 negative	128 per 1,000	81 per 1,000 (67 to 97)	HR 0.63 (0.52 to 0.76)	4038 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Disease-free survival - 5 years follow-up - subgroup analysis by HER2 status - HER2 positive	125 per 1,000	156 per 1,000 (100 to 244)	HR 1.25 (0.80 to 1.92)	567 (1 RCT)	Low	Could not differentiate
Disease-free survival - 8 to 12 years follow-up (all with method of OFS: luteinising-hormone releasing hormone agonists)	198 per 1,000	184 per 1,000 (131 to 261)	HR 0.93 (0.66 to 1.32)	6493 (2 RCTs)	Very low	Could not differentiate
Disease-free survival - 8 years follow-up sensitivity analysis without study with concurrent chemotherapy (TEXT study)	142 per 1,000	135 per 1,000 (99 to 185)	HR 0.95 (0.70 to 1.30)	4886 (2 RCTs)	Very low	Could not differentiate
Disease-free survival - 8 to 12 years follow-up – subgroup analysis by duration of OFS: less than 5 years	130 per 1,000	147 per 1,000 (114 to 189)	HR 1.13 (0.88 to 1.45)	(1 RCT)	Low	Could not differentiate
Disease-free survival - 8 to 12 years follow-up – subgroup analysis by duration of OFS: 5 years	224 per 1,000	177 per 1,000 (157 to 202)	HR 0.79 (0.70 to 0.90)	(1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor
Disease-free survival - 8 years follow-up - subgroup analysis by HER2 status - HER2 negative	173 per 1,000	121 per 1,000 (104 to142)	HR 0.70 (0.60 to 0.82)	4035 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)**	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Disease-free survival - 8 years follow-up - subgroup analysis by HER2 status - HER2 positive	168 per 1,000	198 per 1,000 (134 to 292)	HR 1.18 (0.80 to 1.74)	578 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ** Hazard ratios of less than 1 mean fewer deaths or recurrences. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; HR: risk ratio.

Breast cancer mortality

Table 37 Summary GRADE table for breast cancer mortality

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Breast cancer mortality - 5 years follow-up	295 per 1,000	590 per 1,000 (363 to 959)	HR 2.00 (1.23 to 3.25)	185 (1 RCT)	Low	Effect favours OFS combined with tamoxifen
Breast cancer mortality - 8 to 12 years follow-up	101 per 1,000	91 per 1,000 (75 to 110)	HR 0.90 (0.74 to 1.09)	4941 (2 RCTs)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; HR: risk ratio.

Local and/or locoregional recurrence

Table 38 Summary GRADE table for local and/or locoregional recurrence

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Local and/or locoregional recurrence - 5 years follow-up	25 per 1,000	21 per 1,000 (13 to 34)	RR 0.82 (0.50 to 1.36)	7203 (3 RCTs)	Low	Could not differentiate
Local and/or locoregional recurrence - 8 to 12 years follow-up	47 per 1,000	35 per 1,000 (25 to 52)	RR 0.75 (0.52 to 1.10)	6493 (2 RCTs)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

New contralateral disease

Table 39 Summary GRADE table for new contralateral disease

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
New contralateral disease - 5 years follow-up	12 per 1,000	5 per 1,000 (3 to 9)	RR 0.46 (0.27 to 0.79)	7203 (3 RCTs)	Moderate	Effect favours OFS combined with an aromatase inhibitor
New contralateral disease - 8 to 12 years follow-up	19 per 1,000	14 per 1,000 (9 to 20)	RR 0.74 (0.50 to 1.08)	6493 (2 RCTs)	Moderate	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Adherence to or completion of treatment

Table 40 Summary GRADE table for adherence to or completion of treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Adherence to or completion of treatment (treatment completed at 5 years)	566 per 1,000	600 per 1,000 (469 to 758)	RR 1.06 (0.83 to 1.34)	5400 (2 RCTs)	Very low	Could not differentiate
Adherence to or completion of treatment (treatment completed at 8 years)	865 per 1,000	813 per 1,000 (787 to 830)	RR 0.94 (0.91 to 0.96)	4690 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Quality of life

No evidence identified for this outcome

Adverse events

Table 41 Summary GRADE table for genitourinary adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Vaginal dryness - any grade 5 years follow-up	474 per 1,000	526 per 1,000 (492 to 554)	RR 1.11 (1.04 to 1.17)	4643 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Vaginal dryness - grade 2 5 years follow-up	26 per 1,000	86 per 1,000 (41 to 177)	RR 3.34 (1.61 to 6.91)	713 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Vaginal dryness - any grade 8 years follow-up	492 per 1,000	536 per 1,000 (507 to 571)	RR 1.09 (1.03 to 1.16)	4643 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Incontinence - any grade 5 years follow-up	178 per 1,000	132 per 1,000 (114 to 150)	RR 0.74 (0.64 to 0.84)	4643 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor
Incontinence - grades 3 to 4 5 years follow-up	3 per 1,000	3 per 1,000 (1 to 8)	RR 0.86 (0.29 to 2.55)	4643 (1 RCT)	Low	Could not differentiate
Incontinence - any grade 8 years follow-up	186 per 1,000	136 per 1,000 (119 to 156)	RR 0.73 (0.64 to 0.84)	4643 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Incontinence - grades 3 or 4 8 years follow-up	4 per 1,000	4 per 1,000 (2 to 10)	RR 1.00 (0.40 to 2.52)	4643 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio. **

Table 42 Summary GRADE table for menopausal adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Vasomotor symptoms (hot flushes) - any grade 5 years follow-up	682 per 1,000	669 per 1,000 (655 to 682)	RR 0.98 (0.96 to 1.00)	6446 (2 RCTs)	High	Effect favours OFS combined with an aromatase inhibitor
Vasomotor symptoms (hot flushes) - grade 2 5 years follow-up	234 per 1,000	201 per 1,000 (152 to 266)	RR 0.86 (0.65 to 1.14)	713 (1 RCT)	Low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Vasomotor symptoms (hot flushes) - grades 3 to 4 5 years follow-up	120 per 1,000	100 per 1,000 (85 to 118)	RR 0.83 (0.71 to 0.98)	4643 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor
Vasomotor symptoms (hot flushes) - any grade 8 years follow-up	935 per 1,000	926 per 1,000 (907 to 935)	RR 0.99 (0.97 to 1.00)	4643 (1 RCT)	Low	Effect favours OFS combined with an aromatase inhibitor
Vasomotor symptoms (hot flushes) - grades 3 or 4 8 years follow-up	122 per 1,000	101 per 1,000 (85 to 118)	RR 0.83 (0.70 to 0.97)	4643 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor
Sleep disturbances - any grade 5 years follow-up	452 per 1,000	452 per 1,000 (429 to 475)	RR 1.00 (0.95 to 1.05)	6446 (2 RCTs)	Moderate	Could not differentiate
Sleep disturbances - grade 2 5 years follow-up	11 per 1,000	5 per 1,000 (1 to 30)	RR 0.48 (0.09 to 2.63)	713 (1 RCT)	Low	Could not differentiate
Sleep disturbance - grades 3 to 5 5 years follow-up	43 per 1,000	38 per 1,000 (29 to 51)	RR 0.89 (0.67 to 1.18)	4643 (1 RCT)	Low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Sleep disturbance - any grade 8 years follow-up	595 per 1,000	595 per 1,000 (565 to 624)	RR 1.00 (0.95 to 1.05)	4643 (1 RCT)	Low	Could not differentiate
Insomnia - grades 3 or 4 8 years follow-up	45 per 1,000	38 per 1,000 (29 to 51)	RR 0.85 (0.65 to 1.12)	4643 (1 RCT)	Low	Could not differentiate
Fatigue - any grade - Random-effects model (I2 84%) 5 years follow-up	504 per 1,000	544 per 1,000 (428 to 690)	RR 1.08 (0.85 to 1.37)	6446 (2 RCTs)	Very low	Could not differentiate
Fatigue - grade 2 5 years follow-up	34 per 1,000	5 per 1,000 (1 to 25)	RR 0.16 (0.04 to 0.72)	713 (1 RCT)	Moderate	Effect favours OFS combined with an aromatase inhibitor
Fatigue - grades 3 to 4 5 years follow-up	29 per 1,000	31 per 1,000 (23 to 44)	RR 1.09 (0.79 to 1.51)	4643 (1 RCT)	Low	Could not differentiate
Fatigue - any grade 8 years follow-up	643 per 1,000	624 per 1,000 (598 to 656)	RR 0.97 (0.93 to 1.02)	4643 (1 RCT)	Low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Fatigue - grades 3 or 4 8 years follow-up	30 per 1,000	33 per 1,000 (23 to 45)	RR 1.08 (0.78 to 1.48)	4643 (1 RCT)	Low	Could not differentiate
Weight gain - grade 2 5 years follow-up	17 per 1,000	8 per 1,000 (2 to 33)	RR 0.48 (0.12 to 1.92)	713 (1 RCT)	Low	Could not differentiate
Weight gain - grade 3 5 years follow-up	Not estimable**	Not estimable**	RR 2.91 (0.12 to 71.17)	713 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Absolute effects could not be estimated because there were 0 events in one of the arms. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 43 Summary GRADE table for hypercholesterolemia

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Hypercholesterolemia - grade 2 5 years follow-up	6 per 1,000	19 per 1,000 (4 to 92)	RR 3.39 (0.71 to 16.22)	713 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 44 Summary GRADE table for glucose intolerance

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Glucose intolerance - any grade 5 years follow-up	23 per 1,000	23 per 1,000 (16 to 34)	RR 1.00 (0.69 to 1.46)	4643 (1 RCT)	Low	Could not differentiate
Glucose intolerance - grades 3 to 4 5 years follow-up	6 per 1,000	5 per 1,000 (2 to 10)	RR 0.74 (0.34 to 1.60)	4643 (1 RCT)	Low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Hyperglycaemia - grade 2 5 years follow-up	6 per 1,000	6 per 1,000 (1 to 39)	RR 0.97 (0.14 to 6.85)	713 (1 RCT)	Low	Could not differentiate
Hyperglycaemia - grade 3 5 years follow-up	6 per 1,000	1 per 1,000 (0 to 23)	RR 0.19 (0.01 to 4.03)	713 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 45 Summary GRADE table for neurocognitive adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Depression - any grade 5 years follow-up	375 per 1,000	375 per 1,000 (356 to 397)	RR 1.00 (0.95 to 1.06)	6446 (2 RCTs)	Moderate	Could not differentiate
Depression - grade 2 5 years follow-up	11 per 1,000	25 per 1,000 (8 to 80)	RR 2.18 (0.68 to 7.02)	713 (1 RCT)	Low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Depression - grades 3 to 4 5 years follow-up	39 per 1,000	33 per 1,000 (25 to 43)	RR 0.84 (0.64 to 1.11)	5356 (2 RCTs)	Moderate	Could not differentiate
Depression - any grade 8 years follow-up	514 per 1,000	519 per 1,000 (488 to 545)	RR 1.01 (0.95 to 1.06)	4643 (1 RCT)	Low	Could not differentiate
Depression - grades 3 or 4 8 years follow-up	46 per 1,000	41 per 1,000 (31 to 54)	RR 0.88 (0.67 to 1.16)	4643 (1 RCT)	Low	Could not differentiate
Memory impairment - grade not reported 8 years follow-up	Not estimable**	Not estimable**	RR 12.96 (0.73 to 229.66)	1803 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Absolute effects could not be estimated because there were 0 events in one of the arms. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 46 Summary GRADE table for psychosexual adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Decreased libido - any grade 5 years follow-up	409 per 1,000	449 per 1,000 (421 to 482)	RR 1.10 (1.03 to 1.18)	4643 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Dyspareunia - any grade 5 years follow-up	225 per 1,000	265 per 1,000 (243 to 290)	RR 1.18 (1.08 to 1.29)	5356 (2 RCTs)	High	Effect favours OFS combined with tamoxifen
Dyspareunia - grades 3 to 4 5 years follow-up	14 per 1,000	23 per 1,000 (15 to 35)	RR 1.66 (1.08 to 2.57)	4643 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Decreased libido - any grade 8 years follow-up	422 per 1,000	455 per 1,000 (426 to 485)	RR 1.08 (1.01 to 1.15)	4643 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Dyspareunia - any grade 8 years follow-up	273 per 1,000	317 per 1,000 (290 to 347)	RR 1.16 (1.06 to 1.27)	4643 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Dyspareunia - grades 3 or 4 8 years follow-up	15 per 1,000	24 per 1,000 (16 to 37)	RR 1.61 (1.06 to 2.44)	4643 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 47 Summary GRADE table for musculoskeletal adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Fractures - any grade 5 years follow-up	52 per 1,000	68 per 1,000 (54 to 86)	RR 1.32 (1.05 to 1.66)	4643 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Fractures - grades 3 to 4 5 years follow-up	9 per 1,000	13 per 1,000 (8 to 21)	RR 1.40 (0.88 to 2.23)	6446 (2 RCTs)	Moderate	Could not differentiate
Fracture - any grade 8 years follow-up	60 per 1,000	77 per 1,000 (63 to 96)	RR 1.28 (1.04 to 1.59)	4643 (1 RCT)	Low	Effect favours OFS combined with tamoxifen
Fracture - grade 3 or 4 8 years follow-up	11 per 1,000	16 per 1,000 (10 to 24)	RR 1.46 (0.95 to 2.24)	6446 (2 RCTs)	Moderate	Could not differentiate
Osteoporosis - any grade - Random-effects model 5 years follow-up	197 per 1,000	183 per 1,000 (65 to 513)	RR 0.93 (0.33 to 2.60)	6446 (2 RCTs)	Very low	Could not differentiate
Osteoporosis - grades 3 to 4 5 years follow-up	3 per 1,000	4 per 1,000 (2 to 12)	RR 1.67 (0.61 to 4.59)	4643 (1 RCT)	Low	Could not differentiate
Osteoporosis - any grade 8 years follow-up	279 per 1,000	421 per 1,000 (390 to 457)	RR 1.51 (1.40 to 1.64)	4643 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Osteoporosis - grades 3 or 4 8 years follow-up	3 per 1,000	4 per 1,000 (2 to 11)	RR 1.43 (0.55 to 3.76)	4643 (1 RCT)	Low	Could not differentiate
Arthralgia - any grade 5 years follow-up	426 per 1,000	711 per 1,000 (651 to 775)	RR 1.67 (1.53 to 1.82)	1803 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Arthralgia - grade 2 5 years follow-up	145 per 1,000	294 per 1,000 (216 to 395)	RR 2.02 (1.49 to 2.72)	713 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Arthralgia - grade 3 5 years follow-up	3 per 1,000	33 per 1,000 (4 to 254)	RR 11.64 (1.52 to 89.01)	713 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen
Arthralgia - any grade 8 years follow-up	399 per 1,000	678 per 1,000 (618 to 742)	RR 1.70 (1.55 to 1.86)	1803 (1 RCT)	Moderate	Effect favours OFS combined with tamoxifen

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

Table 48 Summary GRADE table for cardiovascular adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with OFS combined with tamoxifen	Risk with OFS combined with an AI				
Deep vein thrombosis or embolism - grades 3 to 4 5 years follow-up	16 per 1,000	6 per 1,000 (4 to 10)	RR 0.38 (0.23 to 0.64)	6446 (2 RCTs)	High	Effect favours OFS combined with an aromatase inhibitor
Deep vein thrombosis - grade 3 or 4 8 years follow-up	16 per 1,000	6 per 1,000 (4 to 11)	RR 0.38 (0.23 to 0.64)	6446 (2 RCTs)	High	Effect favours OFS combined with an aromatase inhibitor
Cardiac ischaemia or infarction - grades 3 to 4 5 years follow-up	1 per 1,000	3 per 1,000 (1 to 12)	RR 2.34 (0.61 to 9.04)	4643 (1 RCT)	Low	Could not differentiate
Cardiac ischaemia or infarction - grade 3 or 4 8 years follow-up	3 per 1,000	3 per 1,000 (1 to 9)	RR 1.17 (0.39 to 3.48)	4643 (1 RCT)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. AI: aromatase inhibitors; CI: confidence interval; OFS: ovarian function suppression; RR: risk ratio.

See appendix F for full GRADE tables.

1.1.7 Economic evidence

A literature search was conducted to identify published economic evaluations of relevance to the review question on ovarian function suppression (see appendix G). This search retrieved 126 studies, and none of these studies were considered relevant or applicable at title and abstract screening (see Appendix G – Economic evidence study selection).

1.1.8 Summary of included economic evidence

No economic evidence was identified for this review.

1.1.9 Economic model

No original economic modelling was conducted for this review.

1.1.10 Unit costs

Unit costs for the interventions considered in this review are presented in Table 49 and Table 50. Drug costs are taken from the Drugs and pharmaceutical electronic market information tool (eMIT) where possible and otherwise from the British National Formulary (BNF), and dosing information is taken from the BNF. Procedure costs are taken from the NHS National Schedule of Reference costs.

Table 49 Unit costs- endocrine therapies

Resource	Unit costs	Source
Tamoxifen, 20mg tablet	£0.10	eMIT: pack of 30 tablets, weighted average pack price £2.87 (SD £0.36), 20mg per day
Anastrozole, 1mg tablet	£0.02	eMIT: pack of 28 tablets, weighted average pack price £0.50 (SD £1.65), 1mg per day
Letrozole, 2.5mg tablet	£0.03	eMIT: pack of 28 tablets, weighted average pack price £0.86 (SD £0.96), 2.5mg per day
Exemestane, 25mg tablet	£0.14	eMIT: pack of 30 tablets, weighted average pack price £4.20 (SD £7.35), 25mg per day

Table 50 Unit costs - ovarian function suppression

Resource	Unit costs	Source
Goserelin	£70.00	BNF: 3.6mg every 28 days, 3.6mg pre-filled disposable injection
Triptorelin	£69.00	BNF: 3mg every 4 weeks, 3mg vial
Leuprorelin acetate	£75.24	BNF: 3.75mg every month (or 11.25mg every 3 months), 3.75mg pre-filled disposable injection (or 11.25mg pre-filled disposable injection at equivalent price per mg)

Resource	Unit costs	Source
Bilateral oophorectomy	£5,963.70	NHS National Schedule of Reference costs 2021/22: weighted average of cost codes MA08A and MA08B, Major laparoscopic or endoscopic upper genital tract procedures

1.1.11 The committee's discussion and interpretation of the evidence

Terminology in this discussion

- When we mention people with female reproductive organs, we mean this to cover women, trans men and non-binary people who currently have ovaries.
- When we mention people with male reproductive organs, we mean this to cover men, trans women and non-binary people who currently have testes.

1.1.11.1. The outcomes that matter most

The evidence for this review focused on people who are premenopausal or perimenopausal and who have oestrogen receptor (ER) positive invasive breast cancer. In these people, ovarian function suppression (OFS) combined with tamoxifen or OFS combined with an aromatase inhibitor (AI) aims to improve long-term cancer related outcomes. Therefore, the committee agreed that the critical outcomes for this review were overall survival (OS), disease-free survival (DFS) and quality of life, which can be severely affected by the side effects of these treatments.

In addition, the committee acknowledged the importance of other outcomes including mortality due to breast cancer, local and/or locoregional recurrence, and new contralateral disease. Breast cancer mortality was not expected to be widely reported and therefore it was considered important but not critical to decision-making. The risk of local and/or locoregional recurrence and new contralateral disease were included because they could be reduced by treatment with OFS combined with tamoxifen or OFS combined with an aromatase inhibitor.

The committee also noted that the risk of adverse events and types of adverse events that people may experience with these treatments play an important role in their decision-making about whether to accept endocrine treatment, which treatment to take and whether to continue taking it. Therefore, they agreed that specific adverse events (see appendix M) and completion of treatment were also important outcomes for decision making.

1.1.11.2 The quality of the evidence

OFS combined with tamoxifen compared to tamoxifen alone

Most of the included studies reported outcome data for this comparison (9 RCTs). Overall, the outcomes ranged from high to very low quality with the main reasons for downgrading being due to risk of bias, inconsistency and imprecision of the evidence. Some studies were judged to be at moderate or high risk of bias due to poor reporting and concerns about subjective outcomes (these outcomes were quality of

life and adverse events; both mainly reported by participants). Downgrading for inconsistency, where meta-analyses were possible, was due to variability in results between studies for some outcomes, while in other cases evidence came from a single study. Some of the evidence was downgraded once for imprecision as the 95% confidence interval crossed the line of no effect. Studies with a sample size of less than 500 participants were also downgraded for imprecision as there were likely to be too few participants to reliably detect an effect.

The Cochrane systematic review by Bui et al. (2020) was partially applicable and used as source of evidence for this evidence review (only relevant RCTs were included).The RCTs included in this evidence review were all judged to be directly applicable. Although in the ABCTCG 2007 study only 39.1% of participants had ER positive invasive breast cancer, it reported outcome data for this subgroup which was used in our analyses. A similar issue applied to the ZIPP study. Data from the ZIPP study was taken from publications by Baum et al. 2006 and Hackshaw et al. 2009, which presented data for the ER positive population of interest for this review. Therefore, although the results of the full ABCTCG and ZIPP studies were partially applicable the data for people with ER positive breast cancer was deemed to be fully applicable and not downgraded in the GRADE tables.

The majority of the outcome data related to the critical outcomes: overall survival (OS) and disease-free survival (DFS). Local/locoregional recurrence and new contralateral disease were the second most reported outcomes. There was less evidence for quality of life, breast cancer mortality, individual adverse events, and treatment adherence.

The committee had specified that several subgroup analyses be carried out to help them with drafting recommendations. Data was reported for all of these subgroups apart from the one for oestrogen receptor expression levels.

The committee highlighted that chemotherapy can induce menopause and this may confound interpretation of the effectiveness of OFS. The evidence included studies participants receiving concurrent chemotherapy. A sensitivity analysis was carried out removing the ABCTCG study (80% of participants received chemotherapy concurrently with endocrine therapy) for the critical outcomes (overall survival and disease-free survival) to determine if the inclusion of such studies affected the overall estimate of effect.

OFS combined with an aromatase inhibitor compared to tamoxifen alone

Two RCTs reported outcome data for this comparison. Overall, the outcomes ranged from moderate to very low quality with the main reasons for downgrading being due to risk of bias, inconsistency and imprecision of the evidence. These studies were judged to be at moderate or high risk of bias due to poor reporting and concerns about subjective outcomes (these outcomes were adverse events mainly reported by participants). Reasons for downgrading for inconsistency and imprecision were the same as for the analysis above comparing OFS combined with tamoxifen to tamoxifen alone.

Four of the outcomes (OS, DFS, breast cancer mortality local/locoregional recurrence, and new contralateral disease) were only reported by the SOFT study. Treatment adherence and adverse events were only reported as pooled data from

the SOFT and TEXT studies. There was no evidence found on quality of life for this comparison.

The SOFT study reported data for most of the subgroup analysis specified by the committee apart from the subgroup based on oestrogen receptor expression levels. As the SOFT trial participants were intended to take OFS for 5 years and the study only used luteinising-hormone releasing hormone agonists, it was not possible or necessary to carry out these subgroup analyses.

OFS combined with an aromatase inhibitor compared to OFS combined with tamoxifen

Four RCTs reported outcome data for this comparison. Overall, the outcomes ranged from high to very low quality with the main reasons for downgrading being due to risk of bias, inconsistency and imprecision of the evidence. Some studies were judged to be at moderate or high risk of bias due to poor reporting and concerns about subjective outcomes (these outcomes were adverse events mainly reported by participants). Reasons for downgrading for inconsistency and imprecision were the same as for the analysis above comparing OFS combined with tamoxifen to tamoxifen alone.

Three of the studies were judged to be directly applicable but the committee agreed that the ABCSG-12 study was partially applicable. This was because it included zoledronic acid in 2 of the 4 treatment groups along with our treatments of interest but reported pooled data for groups 1 and 2 (OFS combined with tamoxifen with/ without zoledronic acid) compared to pooled data for groups 3 and 4 (OFS combined with an AI with/ without zoledronic acid). The committee noted that zoledronic acid is a bisphosphonate which is usually prescribed to people who are premenopausal or perimenopausal, who have ER positive invasive breast cancer and are taking OFS in combination with tamoxifen or OFS in combination with AI.

The majority of the studies reported data for the critical outcomes OS and DFS, and the important outcomes of local/locoregional recurrence, new contralateral disease and treatment adherence were also well reported. There was less evidence for breast cancer mortality and individual adverse events and no evidence was found on quality of life for this comparison.

As the participants of the 4 included trials were intended to have OFS for at least 5 years and the studies only used luteinising-hormone releasing hormone agonists, it was not possible or necessary to carry out the subgroup analyses for method and duration of OFS. No data on oestrogen receptor expression levels was available so it was not possible to carry out a subgroup analysis on this either. Where data was available, we were able to carry out subgroup analysis for duration of OFS, use of chemotherapy, and HER2 status. The SOFT and TEXT studies were published in a single paper with most of the outcomes of interest being reported as pooled data. However, for the subgroups of interest, the SOFT and TEXT trials provided trial specific data.

As mentioned above, the committee highlighted that chemotherapy can induce menopause which may confound interpretation of the effectiveness of OFS. The evidence included studies participants receiving concurrent chemotherapy. A sensitivity analysis was carried out removing data from the TEXT study (data on participants who received chemotherapy concurrently with endocrine therapy) for the

critical outcomes (overall survival and disease-free survival) to determine if the inclusion of such studies affected the overall estimate of effect.

1.1.11.3 Benefits and harms

OFS combined with tamoxifen compared to tamoxifen alone

The committee discussed the evidence for OFS combined with tamoxifen compared to tamoxifen alone for people who are premenopausal or perimenopausal and who have ER positive invasive breast cancer. They noted that there was a statistically significant improvement in OS at 2.5 to 6 and 8 to12 years (Figure 1 and Figure 8) and DFS at 5 and at 8 to12 years follow-up (Figure 11 and Figure 18) with OFS combined with tamoxifen compared to tamoxifen alone. They agreed that these improvements were large enough to be clinically meaningful (evidence was of high quality.

The results for quality of life were more mixed with it not being possible from the evidence to differentiate or the evidence showing no clinically meaningful difference between OFS combined with tamoxifen compared to tamoxifen alone for FACT-B, FACT-G and all of the International Breast Cancer study group core quality of life form domains reported (Figure 31 and Figure 32). In contrast there was a statistically significant decrease in quality of life with OFS combined with tamoxifen compared to tamoxifen alone relating to menopausal symptoms (from the Postmenopausal Oestrogen/Progestin Intervention checklist) and sexual function (from the Sexual Activity questionnaire). The committee agreed that these differences could be clinically meaningful and were not unexpected as using OFS combined with tamoxifen was intended to induce a menopausal state and this can have adverse effects on sexual function. However, they highlighted that the evidence was of low quality and were less confident in the significance of these results.

Subgroup analyses were carried out for OS and DFS where there was data available (duration of OFS, method of OFS, lymph node status, use of chemotherapy and HER2 status). For DFS there was also data on age. No subgroup differences were detected for all of the subgroup analyses apart from the HER2 status subgroup.

For OS (Figure 10) and DFS (Figure 17) there was a statistically significant difference in effect between subgroups for the analysis based on HER2 status. In both cases, for people with HER2 negative tumours it was not possible from the evidence to differentiate between OFS combined with tamoxifen compared to tamoxifen alone, but for people with HER2 positive tumours there was a statistically significant effect showing improved OS (low quality evidence) and DFS (moderate quality evidence) with OFS combined with tamoxifen compared to tamoxifen alone. For OS, the data for people with HER2 positive tumours came from the SOFT study. This study reported that only 60% of participants with HER2 positive tumours received anti-HER2 treatment. The committee noted that this study was carried out around the time that the anti-HER2 treatment trastuzumab was being introduced into clinical practice, with randomisation of participants happening from December 2003 through January 2011. (The NICE TA for trastuzumab was published in 2006.) They highlighted that the use of an anti-HER2 treatment by some participants but not all complicates interpretation of this subgroup analysis because improved outcomes are expected with targeted treatment for people with HER2 positive tumours.

For DFS, the results for the subgroup of people with HER2 positive tumours were based on data from the SOFT and ASTRRA studies. Both studies included the use of anti-HER2 treatments. The ASTRRA study does not report what proportion of participants were taking anti-HER2 therapies (but these were allowed and used according to the policy of each institution) and it enrolled patients between March 2009 and March 2014. The same issues applied as for the OS results. Therefore, the committee did not make a specific recommendation for people with HER2 positive tumours.

The committee discussed the timing of chemotherapy treatment in relation to OFS and the potential effect this could have on the effectiveness of OFS treatment combined with tamoxifen. They noted that in some of the studies chemotherapy was given before OFS combined with tamoxifen and that chemotherapy could induce menopause temporarily or permanently (or the individual could enter menopause naturally during treatment). They agreed that for people taking chemotherapy before OFS, the benefits of OFS are confined to people who return to premenopausal or perimenopausal status after chemotherapy. All of the included studies specified that participants had to be premenopausal to be enrolled, but this was defined in a range of ways. For example, as having a last menstrual cycle within 12 months prior to randomisation or having regular vaginal bleeding at the time of diagnosis. The SOFT trial specified that people had to have regular menses without exogeneous hormones during prior 6 months and/or oestradiol level in the premenopausal range. In many other cases it was unclear whether the criteria the studies used would have excluded people who were no longer premenopausal or perimenopausal following chemotherapy treatment.

One study, ABCTCG, allowed concurrent chemotherapy with OFS combined with tamoxifen or tamoxifen alone and the committee noted that this could have induced a menopausal status in people in the tamoxifen arm of the study potentially reducing the difference in effect between the study arms. A sensitivity analysis was carried out (Figure 2) to look at the effect of excluding this study from the OS analysis (this study did not report DFS). The results of this analysis were very similar to that of the main analysis and the interpretation of effect was maintained. Subgroup analyses were also carried out looking at the effect of having prior or concurrent chemotherapy (chemotherapy yes) compared to no chemotherapy for OS and DFS, but no subgroup differences were detected. The committee highlighted that chemotherapy is usually given to people at higher risk of recurrence. They also noted that in their experience, chemotherapy is more effective now than at the time the trials were conducted.

There was limited evidence for breast cancer mortality. It was not possible from the low quality evidence from a single study to differentiate between OFS combined with tamoxifen compared to tamoxifen alone (Figure 25). It was also not possible from the evidence to differentiate between OFS combined with tamoxifen compared to tamoxifen alone for new contralateral disease at 5 (moderate quality evidence) and at 8 to 12 years (very low quality evidence) follow-up (Figure 28 and Figure 29). However, local/locoregional recurrence was statistically significantly reduced with OFS combined with tamoxifen compared to tamoxifen alone at 5 and at 8 to 12 years follow-up and this was judged to be a clinically meaningful effect from high quality evidence (Figure 26 and Figure 27).

Treatment adherence was statistically significantly improved with OFS combined with tamoxifen compared to tamoxifen alone at 5 years follow-up (Figure 30). Although this was judged to be a clinically meaningful effect and with high quality evidence, the committee noted that this result was not what they expected, because they expected adherence to be lower with OFS combined with tamoxifen due to increased side effects. However, they noted that adherence may have been improved by people usually seeing a health professional to receive OFS treatment. They also noted that participants in clinical trials may be more motivated to adhere to treatment. It was unclear whether this finding would be reflected in the real life.

The committee also discussed the evidence for harms (Figure 33 to Figure 47) and noted that there were statistically significant and clinically meaningful (mainly moderate quality evidence) increased risks of the following adverse events with OFS combined with tamoxifen compared to tamoxifen alone: vaginal dryness (any grade); vasomotor symptoms (hot flushes, grade 3); sleep disturbances or insomnia (any grade); glucose intolerance (any grade and grade 3 to 4); depression (any grade); decreased libido or dyspareunia- (any grade) and osteoporosis (any grade). They noted that although there were some grade 3 to 4 events reported, grade 3 events are usually severe enough to require hospitalisation and grade 4 are life threatening. Grade 3 or 4 events would not be expected to occur for many of the adverse events of interest here. For the same reason 'any grade' adverse events were expected to be mainly comprised of grade 1 to 3 events and not include grade 4 adverse events in most cases. The committee noted that although grade 3 events are classed as serious and interfering with a person's ability to function, some grade 1 or 2 adverse events may also have a substantial negative impact on quality of life for some people. The committee also agreed that although other grade 1 or 2 events may not have a substantial negative impact on quality of life on their own, as these events usually occur with other adverse events, their combined negative impact on quality of life can be severe.

Most of these adverse events were not unexpected as they were linked to the induction of menopause and the committee agreed that in their experience side effects were worse when OFS combined with tamoxifen is used compared to tamoxifen alone. However, the committee noted that glucose intolerance is not something they routinely screen for in this population. Glucose intolerance and diabetes were included as adverse events by the SOFT study because the authors found that increased risk of diabetes was suggested by epidemiologic studies in men who were receiving gonadotropin-releasing hormone (GnRH) for prostate cancer (references were not provided for these epidemiologic studies).

OFS combined with an aromatase inhibitor compared to tamoxifen alone

The committee discussed the evidence for OFS combined with an aromatase inhibitor (AI) compared to tamoxifen alone for people who are premenopausal and who have ER positive invasive breast cancer. For OS it was not possible from the evidence to differentiate (low quality evidence) between OFS combined with an AI compared to tamoxifen alone at 5 years and 12 years follow up (Figure 48 and Figure 50). In contrast, there was a statistically significant improvement in DFS with OFS combined with an AI compared to tamoxifen alone at 5 years and that this was also seen at 12 years follow up (Figure 53 and Figure 56). They agreed that these improvements were large enough to be clinically meaningful and that evidence was of moderate quality. Subgroup analyses were carried out for OS and DFS where there was data, but no subgroup differences were detected for any of these analyses.

It was not possible from the evidence to differentiate between OFS combined with an AI compared to tamoxifen alone for breast cancer mortality at 12 years (low quality evidence) follow-up (Figure 59) and for treatment adherence at 8 years (low quality evidence) follow-up (Figure 62). However, local/locoregional recurrence and new contralateral disease were statistically significantly reduced with OFS combined with an AI compared to tamoxifen alone at 12 years follow-up (Figure 60 and Figure 61, respectively). These were judged to be clinically meaningful effects and based on moderate quality evidence.

The committee also discussed the evidence for harms (Figure 63 to Figure 76) from OFS combined with an AI compared to tamoxifen alone and noted that there were statistically significant and clinically meaningful (moderate quality evidence) increased risks of the following adverse events with OFS combined with an AI compared to tamoxifen alone: vaginal dryness (any grade); vasomotor symptoms (hot flushes, any grade and grades 3 to 4); sleep disturbances (any grade); depression (any grade); dyspareunia (any grade); fractures (any grade) and osteoporosis (any grade.) There was a statistically significant and clinically meaningful decreased risk of thrombosis or embolism (grades 3 to 4) with OFS combined with an AI compared to tamoxifen alone.

OFS combined with an aromatase inhibitors compared to OFS combined with tamoxifen

The committee discussed the evidence for OFS combined with an AI compared to OFS combined with tamoxifen for people who are premenopausal and who have ER positive invasive breast cancer. It was not possible from the evidence to differentiate between OFS combined with an AI compared to OFS combined with tamoxifen alone at 5 years and 12 years follow up for OS (Figure 77 and Figure 80) or DFS (Figure 86 and Figure 93). This may be because there is no clinically meaningful difference between the 2 interventions in their effect on OS or the difference in effect between the interventions may be small and hard to detect even with a relatively large sample size in the meta-analysis (very low quality evidence for both follow up times).

The committee were aware of research looking at the effectiveness of AI in post-menopausal women. Recurrence of breast cancer in post-menopausal women was significantly reduced with AI compared to tamoxifen (EBCTCG 2015). The committee noted that OFS mimics post-menopausal status. Based on this they expected that OFS combined with an AI would be more effective than OFS combined with tamoxifen in premenopausal women. They noted that the biggest RCTs (SOFT and TEXT, pooled data reported) showed a statistically significant improvement in DFS with OFS combined with an AI compared to OFS combined with tamoxifen (at both follow-up times). The committee agreed to place more weight on the results of the SOFT and TEXT studies because these trials had much larger numbers of participants than the other trials and were deemed to be at low risk of bias for all outcomes apart from adverse events. They agreed that the level of improvement in DFS seen in the SOFT and TEXT trials would be clinically meaningful.

Subgroup analyses were carried out for OS and DFS where there was data, but no subgroup differences were detected for any of the analyses apart from the HER2 subgroup analyses, where there was a statistically significant difference in effect for the subgroup for OS (Figure 85) at 8 years, and DFS at 5 years (Figure 92) and 8 years (Figure 99) based on data reported by the SOFT and TEXT studies. For both

outcomes, it was not possible from the evidence to differentiate between OFS combined with an AI compared to OFS combined with tamoxifen for people with HER2 positive tumours, but for people with HER2 negative tumours there was a statistically significant improvement in OS (moderate quality evidence) and DFS (moderate quality evidence) with OFS combined with an AI compared to OFS combined with tamoxifen. As discussed above (see the section on OFS combined with tamoxifen compared to tamoxifen alone) the interpretation of this effect was complicated by the timing of the SOFT study and that only 60% of participants used anti-HER2 treatments. The committee therefore decide not to make separate recommendations based on HER2 status. However, they noted that for people with HER2 negative tumours, OFS combined with an AI may be a more effective treatment option in terms of improving OS and DFS.

One study, TEXT, allowed concurrent chemotherapy with OFS combined with an AI or OFS in combination with to tamoxifen and the committee noted that this could have induced a menopausal status. However, as both groups received OFS with the aim of inducing menopausal status, chemotherapy-induced menopause is not expected to have an impact on the difference in effect between the two groups. A sensitivity analysis was carried out to look at the effect of excluding this study from the OS analysis (Figure 81) and from the DFS analysis (Figure 87 and Figure 94). The results of this analysis were very similar to that of the main analysis and the interpretation of effect was maintained. Subgroup analyses were also carried out looking at the effect of having prior or concurrent chemotherapy (chemotherapy yes) compared to no chemotherapy for OS and DFS, but no subgroup differences were detected. The committee highlighted that chemotherapy is usually given to people at higher risk of recurrence. They also noted that in their experience, chemotherapy is more effective now than at the time the trials were conducted.

The committee noted that the results for the other outcomes were mixed with some favouring the use of OFS combined with an AI, some favouring OFS combined with tamoxifen and others where it was not possible from the evidence to differentiate between the 2 comparators. Breast cancer mortality was statistically significantly lower with OFS combined with tamoxifen compared to OFS combined with an AI at 5 years (low quality evidence) but not at 8 to 12 years (low quality evidence) follow up (Figure 100 and Figure 101). It was not possible from the evidence to differentiate between OFS combined with an AI compared to OFS combined with tamoxifen for local/locoregional recurrence at 5 years (low quality evidence) and at 8 to 12 years (low quality evidence) follow up (Figure 102 and Figure 103). New contralateral disease was statistically significantly lower with OFS combined with an AI compared to OFS combined with tamoxifen at 5 years (moderate quality evidence) but not at 8 to 12 years (moderate quality evidence) (Figure 104 and Figure 105). Treatment adherence was statistically significantly lower with OFS combined with an AI compared to OFS combined with tamoxifen at 8 years (moderate quality evidence) but not at 5 years (very low quality evidence) follow-up (Figure 107 and Figure 106).

The committee discussed the evidence about side effects and noted that there were statistically significant increased risks of some adverse events (mainly from moderate quality evidence) with OFS combined with an AI compared to OFS combined with tamoxifen. These were vaginal dryness (grade 2), decreased libido (any grade), fractures (any grade), dyspareunia (any grade), osteoporosis (any grade) and arthralgia (any grade, grade 2 and grade 3). In contrast, the risk of the following adverse events was reduced with OFS combined with an AI compared to OFS

combined with tamoxifen: incontinence (any grade), vasomotor symptoms (hot flushes, grades 3 to 4), fatigue (grade 2), deep vein thrombosis or embolism (grade 3 or more). (See Figure 108 to Figure 135 for grades of adverse events and follow up times.) The committee noted that although the risk of having some side effects may be higher with one combination treatment than the other, there is some uncertainty around these specific results because the current analysis was not designed to look at this issue definitively.

Drafting the recommendations

In 2018 the committee made a recommendation to consider ovarian function suppression combined with other endocrine therapy for premenopausal women with ER positive invasive breast cancer and to discuss the benefits and risks of this treatment option. The recommendation did not specify the type of endocrine therapy and the evidence underpinning the recommendation came from studies that used OFS combined with tamoxifen only. There was no data for OFS combined with an AI at that time.

The evidence presented to the current committee was mainly for studies that used OFS combined with tamoxifen compared to tamoxifen alone, although there were some studies that looked at OFS combined with an AI compared to tamoxifen alone, or OFS combined with an AI compared to OFS combined with tamoxifen. The committee were confident that the evidence in 2024 was stronger than in 2018 as there were more included studies for OFS combined with tamoxifen compared to tamoxifen alone and evidence for improvements in OS and DFS, and reductions in local and/or locoregional recurrence were seen at 5 years and 8 to 12 years follow-up. For OFS combined with an AI compared to tamoxifen alone, improvement in DFS, but not OS, were seen at 5 years and 8 to 12 years follow-up, with reductions in local and/or locoregional recurrence and new contralateral disease. The committee acknowledged that there was also an increased risk of menopausal-related, psychosexual and genitourinary adverse events as well as osteoporosis, and depression with these treatments compared to tamoxifen alone, which can impact on quality of life. Taking these findings into account the committee agreed that both treatment options were sufficiently effective that they could recommend them but that it is important that patients are aware of potential side effects.

Based on the evidence from this review, the committee were less certain about whether OFS combined with tamoxifen or OFS combined with an AI was more effective as it was not possible from the evidence to differentiate between them for OS and DFS. For the other outcomes of interest, it was also not possible from the evidence to differentiate between treatments or there was no clear pattern to the results. For example, breast cancer mortality was reduced with OFS combined with tamoxifen compared to OFS combined with an AI, but new contralateral disease was reduced with OFS combined with an AI compared to OFS combined with tamoxifen, both at 5 years follow up, while it was not possible from the evidence to differentiate between treatments at 8 to 12 years for both outcomes. The committee therefore decided against recommending one of these treatment combinations over the other. However, they were aware of evidence (see section above on ‘OFS combined with an aromatase inhibitor compared to OFS combined with tamoxifen’) about the effectiveness of AI alone in comparison to tamoxifen alone in post- menopausal women and based on this they expected that OFS combined with an AI would be more effective than OFS combined with tamoxifen in premenopausal women. This

was reflected by the results of the SOFT trial comparing OFS combined with an AI to OFS combined with tamoxifen for DFS.

In addition to the 2018 recommendation about using endocrine therapy with ovarian function suppression combined with tamoxifen or an AI for premenopausal women with ER positive invasive breast cancer, the guideline included a recommendation to offer tamoxifen as the initial adjuvant endocrine therapy for men and premenopausal women with ER-positive invasive breast cancer. The committee did not look at the evidence around using endocrine therapy in men and so agreed that this recommendation be retained for this specific population. However, the current review did impact on the recommendation where it concerned premenopausal women (now called people to be more inclusive). The committee agreed that based on the evidence in this review, they would not necessarily recommend tamoxifen as the initial endocrine therapy for these people. Instead, this decision would be made as part of the discussion covered by their new recommendation. They therefore decided to split this recommendation into 2 parts to cover men and premenopausal people separately. They agreed that there was strong evidence from the 2018 review on endocrine therapy and the current review on OFS combined with an AI or OFS in combination with tamoxifen that people who are premenopausal or perimenopausal with ER-positive invasive breast cancer should be offered endocrine therapy, but that the choice of this therapy (OFS combined with an AI or OFS in combination with tamoxifen or tamoxifen alone) should be made as part of a shared decision making process covered by their new recommendation.

The committee also noted the increased risk of adverse events was higher with OFS combined with tamoxifen or OFS combined with an AI compared to tamoxifen alone. These were mainly, but not all, menopause related and included vaginal dryness, incontinence, hot flushes, sleep disturbances or insomnia, glucose intolerance, depression, decreased libido or dyspareunia, fractures, osteoporosis and arthralgia. The committee acknowledged that for some people the benefits of having OFS combined with tamoxifen or OFS combined with an AI in terms of improved survival and reduced recurrence may not outweigh the increased risk of adverse events associated with these treatments. This could be the case for people who are at low risk of recurrence. However, although the committee thought that people at higher risk of recurrence were likely to receive more benefit from having OFS combined with tamoxifen or OFS in combination with an AI, they decided against limiting their recommendation to this population because people at lower risk of recurrence may also derive some benefit from these treatments compared to taking tamoxifen alone and may wish to have the option of taking them.

The committee agreed that there should be a balance between clinical outcomes and patient-reported outcomes when making decisions about adjuvant endocrine therapy. However, the evidence on quality of life was limited and the committee had to use their own expertise to try to fill this gap. As mentioned above, there was extensive data on adverse events which was used to help inform discussions about the impact of these treatments on people with ER positive invasive breast cancer. In addition, the committee included lay members who were able to bring their own experiences of, and that of people in the patient networks they are involved in, of using these treatments to the discussions. In particular, they supported the view of the clinicians that a discussion should take place about the benefits and risks of adjuvant endocrine therapy for people who are premenopausal or perimenopausal with ER positive invasive breast cancer. As a result, the committee phrased their

recommendation as a shared decision to be made with the person who has with ER positive invasive breast cancer and is premenopausal or perimenopausal about what type of endocrine therapy would be suitable for them as an individual. They also included a bullet point to acknowledge that the use of ovarian function suppression may be most beneficial for people who are at higher risk of disease recurrence. The recommendation was supported by a table showing the benefits and harms associated with OFS combined with tamoxifen compared to tamoxifen alone; OFS combined with an AI compared to tamoxifen alone; and OFS combined with an AI compared to OFS combined with tamoxifen.

The committee were aware that some of the side effects of treatment with OFS combined with tamoxifen or OFS combined with an AI or tamoxifen alone could be mitigated by other treatments, such as lubricants or vaginal moisturisers to reduce vaginal dryness, and therefore do not have to be a barrier to accepting these treatment options or continuing to take them. They agreed that people should be made aware of the possible side effects of each treatment option, including what to expect and how these could be managed if they develop and included this in the shared decision making recommendation.

The committee highlighted that perimenopausal people were not excluded by any of the included trials and that most of these trials defined premenopausal status in a way that could be interpreted that perimenopausal people were also included. Therefore, the committee agreed that the evidence was applicable to perimenopausal people.

OFS combined with tamoxifen or OFS combined with an AI was reported in the included studies with the longest follow up being 12 years. The committee highlighted that the long-term consequences of these treatments and effects on quality of life due to inducing the menopause prematurely are unclear. They agreed that data from real-world evidence could provide clarity on these long-term consequences from studies with follow-up 15 years and longer. Therefore, the committee made a recommendation for research to gather evidence on this topic.

1.1.11.4 Cost effectiveness and resource use

No health economic studies were identified and *de novo* economic modelling was not undertaken for this review question.

The committee were presented with costs of different treatment regimens. The cost of tamoxifen and aromatase inhibitors were shown to have a low cost per day (tamoxifen estimated to cost around £34.95 a year and aromatase inhibitors between £6.52 and £51.14 a year). The overall costs were relatively similar to each other and therefore unlikely to drive the relative cost effectiveness of aromatase inhibitors or tamoxifen containing regimens. The combination of OFS with an AI or tamoxifen regimens would constitute the cost of the monthly or 3-monthly injection and would also include an appointment with a nurse for administration (£8.83 for a 10-minute appointment). The committee explained how surgical OFS (oophorectomy) are rarely undertaken but that bilateral oophorectomy is still offered to some patients in clinical practices, and OFS is more commonly achieved via hormone therapy injections.

The clinical review found that endocrine therapy with OFS would lead to favourable outcomes compared to tamoxifen alone with respect to recurrence. However, it is

associated with an increased risk of menopausal-related, psychosexual and genitourinary adverse events as well as osteoporosis, depression and hot flushes. The committee then discussed the relative costs and impact to patients of experiencing a recurrence and an adverse event.

The average cost of a localised and a distant recurrence were estimated as £17,136 and £18,389, respectively, and were estimated from information in TA886 on olaparib and the National Disease Registration Service (NDRS). The costs reflect the proportion of people who would receive treatment for each type of recurrence with radiotherapy, surgery and systemic anti-cancer therapy, which was assumed to be palbociclib, abemaciclib or ribociclib plus fulvestrant over a median of 10 cycles. Evidence suggests that if 1,000 people receive tamoxifen alone, 65 people will experience recurrence, compared to 36 people experiencing recurrence out of 1,000 people receiving OFS combined with an aromatase inhibitor.

Many of the adverse events are expected to be self-managed, incurring the cost of a GP visit (£45 for a 10 minute consultation), or managed via low cost prescriptions (e.g. bisphosphonates for osteoporosis at high risk of fractures, costing up to £250 per year, or venlafaxine for menopausal symptoms at £3.29 per month). Some of the events with a statistically significant difference in risk between treatment strategies, specifically hot flushes and glucose intolerance, were grade 3 to 4 and could be associated with hospitalisation and significant impact on quality of life. Non-diabetic hyperglycaemia can cost up to £2,225 per year, but these were relatively rare events and so unlikely to contribute to overall costs attributed to the treatment strategy.

The committee noted that it is typically more expensive to manage a recurrence than an adverse event, and we would expect that a recurrence is more likely to have further consequences and impact QoL. Therefore, endocrine therapy combined with OFS is likely to be a cost-effective strategy compared to tamoxifen alone in those at higher risk of recurrence.

Endocrine therapy with or without OFS is already current practice in the UK for ER positive breast cancer. The recommendation may increase the number of people receiving OFS given the stronger available evidence for it and might lead to an initial increase in NHS spending on OFS and its associated administration by nurses every one to three months. However, downstream savings caused by fewer recurrences will likely offset the higher pharmaceutical costs.

1.1.11.5 Other factors the committee took into account

The committee noted that, in the 2018 version of this guideline, there were separate recommendations to offer endocrine therapy to people with ER-positive invasive breast cancer who are premenopausal or perimenopausal or who have male reproductive organs, and for people who are postmenopausal. They agreed that it would be clearer to have a single overarching recommendation on endocrine therapy before giving advice about which therapy is suitable for each population separately, and so revised the recommendations accordingly.

The committee noted that the equality and health inequalities assessment that accompanies this review highlighted a large number of issues that could affect people who are premenopausal or perimenopausal and who have ER positive invasive breast cancer constraining their decisions about whether to take endocrine

therapy and which type to choose (tamoxifen alone or OFS combined with tamoxifen or OFS combined with an AI. However, they noted that many of these issues were societal and not within the committee's ability to address. For example, problems associated with being able to afford to take time off work and having access to affordable transport to take them to appointments or limited availability of healthcare facilities and long waiting times in their local areas. However, they noted that there are local initiatives in some places that provide free transport and extended or weekend hours that may help those who require this type of support.

Some of the issues related to communication of information in a way that is accessible for people with a range of needs (including those with low health literacy, people who have severe learning disabilities, people who are neurodiverse). The committee had previously drafted a new recommendation in the systemic anti-cancer therapy planning section of NG101 (as part of review O on neoadjuvant chemotherapy) that provides links to core NICE guidelines aimed at facilitating the decision-making process and ensuring that patients are able to fully participate. These were the sections on enabling patients to actively participate in their care in the NICE guideline on patient experience in adult NHS services, and communicating risks, benefits and consequences in the NICE guideline on shared decision making.

Some groups, such as people with learning disabilities and autism, may need reasonable adjustments to be made to overcome barriers to access and enable them to make informed decisions. The committee noted that making reasonable adjustments is a legal requirement as stated in the Equality Act 2010. They also noted that there is a newly released Reasonable Adjustment Digital Flag (RADF) and Information Standard. This mandates the identification of people who need reasonable adjustments and the recording, sharing and maintenance of this information with relevant health care providers. The committee also agreed that factors such as having physical or learning disabilities or comorbidities should not prevent someone from being offered tamoxifen or OFS combined with tamoxifen or OFS combined with an AI. However, they acknowledged that these people may need additional support to overcome any barriers they face to taking up the offer if they decide that it is the right option for them.

The committee also noted the importance of discussing the person's preferences and asking about their personal circumstances as part of the discussions around treatment choice. They were aware that, in addition to clinical factors (including effects on OS, DFS and the risk of adverse events and their impacts on quality of life), there are a range of factors that will influence a person's choice of whether to have adjuvant endocrine therapy and the type of endocrine therapy. One such factor that was discussed was around how OFS was administered as the committee noted that this could require monthly or three-monthly injections. This might affect the choice of treatment for people who have childcare and other caring responsibilities, or those who will have to take unpaid time off from work.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendation 1.7.2 and the research recommendation on the long-term adverse events and effects on quality of life using OFS combined with tamoxifen or an AI.

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1.1.13 References – included studies

1.1.13.1 Effectiveness

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Ribi, Karin, Luo, Weixiu, Bernhard, Jurg et al. (2016) Adjuvant Tamoxifen Plus Ovarian Function Suppression Versus Tamoxifen Alone in Premenopausal Women With Early Breast Cancer: Patient-Reported Outcomes in the Suppression of Ovarian Function Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34(14): 1601-10

Sun, Dan; Li, Yingchun; Zhang, Xiaoyu (2021) Role of leuprorelin on ovarian function of patients with receptor-positive premenopausal breast cancer. Pakistan journal of pharmaceutical sciences 34(6supplementary): 2379-2383

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1.1.13.2 Economic

No evidence identified.

1.1.14 References – other

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Appendices

Appendix A – Review protocols

Review protocol for endocrine therapy using tamoxifen or aromatase inhibitors combined with ovarian function suppression in people with oestrogen receptor (ER) positive invasive breast cancer who have female reproductive organs and are premenopausal or perimenopausal

ID	Field	Content
1.	Review title	Endocrine therapy using tamoxifen or aromatase inhibitors combined with ovarian function suppression in people with oestrogen receptor (ER) positive invasive breast cancer that is local or locally advanced and who have female reproductive organs and are premenopausal or perimenopausal.
2.	Review question	What is the clinical and cost effectiveness of ovarian function suppression combined with endocrine therapy using tamoxifen or aromatase inhibitors in people with oestrogen receptor positive invasive breast cancer that is local or locally advanced who have female reproductive organs and are premenopausal or perimenopausal?
3.	Objective	To assess the clinical and cost effectiveness of ovarian function suppression combined with endocrine therapy in people with ER positive invasive breast cancer that is local or locally advanced who have female reproductive organs and are premenopausal or perimenopausal.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistimonikos • MEDLINE ALL For the economics review the following databases will be searched: • Embase • MEDLINE ALL • Econlit • INAHTA • NHS EED Searches will be restricted by: • English language • Human studies • Abstracts, conference presentations, and theses will be excluded.

		• Systematic reviews and RCTs The full search strategies will be published in the final review.
5.	Condition or domain being studied	Oestrogen receptor positive invasive breast cancer in people who have female reproductive organs and are premenopausal or perimenopausal. The breast cancer is of any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0).
6.	Population	Inclusion: • Adults (18 and over) with invasive ER positive breast cancer and female reproductive organs who are premenopausal or perimenopausal. The invasive breast cancer is of any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0). Exclusion: • Adults (18 and over) with: • invasive ER positive breast cancer and female reproductive organs who are postmenopausal • invasive breast cancer that is not ER positive. • metastatic breast cancer (covered by CG81 currently). • newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Paget's disease of the breast with no invasive component.
7.	Intervention	Ovarian function suppression combined with other endocrine therapy (either aromatase inhibitors* or tamoxifen) Ovarian function suppression using: • Luteinising-hormone releasing hormone (LHRH) agonists of interest: buserelin, goserelin, leuprorelin, nafarelin, and triptorelin. These have to be used for at least 12 months. • Oophorectomy (bilateral) *Aromatase inhibitors of interest: anastrozole, exemestane and letrozole.
8.	Comparator	• Ovarian function suppression combined with endocrine therapy using aromatase inhibitors compared to ovarian function suppression combined with tamoxifen • Tamoxifen without ovarian function suppression compared to ovarian function suppression combined with an aromatase inhibitor or ovarian function suppression combined with tamoxifen
9.	Types of study to be included	• Systematic reviews/meta-analyses of RCTs • RCTs
10.	Other exclusion criteria	• Abstracts, conference presentations, theses and narrative reviews • Non-human studies

		• Non-English language studies • Studies where the LHRH agonists have been used for <12 months.
11.	Context	The current advice focuses on considering ovarian function suppression combined with another endocrine therapy, as part of the treatment for breast cancer, in premenopausal women with ER positive early or locally advanced invasive breast cancer. The recommendations are based on evidence from studies where ovarian function suppression (a type of gonadal function suppression) was given combined with tamoxifen as an endocrine therapy. New evidence identified by the 2023 surveillance review indicates that ovarian function suppression combined with an aromatase inhibitor may be a suitable or better alternative than ovarian function suppression combined with tamoxifen. The evidence in this area will be reviewed as part of this update. This update will not look at ovarian function suppression as a means of preserving fertility during treatment for breast cancer.
12.	Primary outcomes (critical outcomes)	• Overall survival (time to event data) • Disease-free survival (time to event data) • Quality of life (using validated measures such as the EQ-5D, FACT-G, FACT-B [and derivatives] and WHOQOL-100; MID: values from the literature where available) **Minimal important differences** Quality of life MID values from the literature: • EQ-5D: 0.08 for UK-based scores and 0.07 for VAS scores • FACT-G total: 3-7 points • FACT-B total: 7-8 points • TOI (trial outcome index) of FACT-B: 5-6 points • BCS of FACT-B: 2-3 points • WHOQOL-100: 1 point Any statistically significant difference will be used for overall survival and disease-free survival. **Time points** Data for the longest follow-up time will be extracted if multiple time points are reported.

13.	Secondary outcomes (important outcomes)	• Breast cancer mortality (time to event data)
		• Adverse events (dichotomous outcome)
		  ○ treatment-related mortality
		  ○ treatment-related morbidity (specific adverse outcomes of interest only)(dichotomous outcome) (See appendix M for table with AEs of interest)
		• Local and/or locoregional recurrence (dichotomous outcome)
		• New contralateral disease (dichotomous outcome)
		• Adherence to or completion of treatment (early cessation of treatment; dichotomous outcome)

		Minimal important differences Any statistically significant difference will be used for all important outcomes. **Time points** Data for the longest follow-up time will be extracted if multiple time points are reported.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias for RCTs and systematic reviews will be assessed using the Cochrane Risk of Bias v.2.0 or ROBIS respectively, as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Where possible, meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions. Hazard ratios will be pooled using the generic inverse-variance method. Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Continuous outcomes will be analysed as mean differences, unless multiple scales are used to measure the same factor. In these cases, standardised mean differences (SMDs) will be used instead. Any pooled SMDs will be back converted to a suitable scale to aid committee interpretation. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions is met: • Significant between-study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. GRADE will be used to assess the quality of the outcomes. Data from randomised controlled trials will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias.

17.	Analysis of subgroups	Subgroups will be carried out where possible, for overall survival and disease-free survival (critical outcomes) only: • Age (under 40, 40 and over) • Duration of OFS (1-<5, ≥5, if not possible then <3 years vs ≥ 3 years) • Lymph node status (positive/negative) (NB: we will note if this is reported before or after chemotherapy) • Method of OFS used with tamoxifen or aromatase inhibitor (surgery versus LHRH agonists) • Chemotherapy use (yes/no) • HER2 status (positive/negative) • ER levels (low or high)
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	August 2024
22.	Anticipated completion date	April 2025
23.	Named contact	**5a. Named contact** NICE Topic Hub 1 **5b Named contact e-mail** breastcancerupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)
24.	Review team members	• Marie Harrisingh, Topic Lead • Sarah Boyce, Senior technical analyst • Yolanda Martinez, Technical analyst • Nancy Pursey, Assistant technical analyst • Lindsay Claxton, Health economics Adviser • Hannah Tebbs, Senior technical health economist • Andrea Heath, Information specialist • Gareth Haman, Editor

25.	Funding sources/sponsor	This systematic review is being completed by NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Early and locally advanced breast cancer: diagnosis and management - Neoadjuvant chemotherapy and ovarian function suppression (update).
28.	Other registration details	None
29.	Reference/URL for published protocol	N/A
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
31.	Keywords	Ovarian function suppression, breast cancer, aromatase inhibitors, tamoxifen
32.	Details of existing review of same topic by same authors	N/A
33.	Additional information	None
34.	Details of final publication	www.nice.org.uk

1

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. The searches were run on 12 August 2024 and the cost effectiveness searches were run on 15 August 2024.

This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was adapted from the original NG101 search but changed structurally due to the slight change to the review question.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations

- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

No date limits were applied to the effectiveness search in adherence to the review protocol. A date limit of 2010 to date was applied for the cost effectiveness search.

Search filters and classifiers

Effectiveness searches

Randomised controlled trials filter

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.

The standard NICE modifications were used: the MeSH heading *randomized controlled trial/*, which is equivalent *to randomized controlled trial.pt* was exploded to capture newer, narrower *terms equivalence trial/ and pragmatic clinical trial*. The free-text term *randomized.mp* was also changed to the (more inclusive) alternative *randomi?ed.mp.* to capture both UK and US spellings.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

Cost effectiveness searches

The following search filter was applied to the search strategies in MEDLINE and Embase to identify cost effectiveness studies:

> Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

Translations of the databases for the effectiveness and cost-effectiveness searches were done as appropriate to the size and interface of the individual databases.

Effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	12/08/24	Wiley	Cochrane Central Register of Controlled Trials Issue 7 of 12, July 2024	372
Cochrane Database of Systematic Reviews (CDSR)	12/08/24	Wiley	Cochrane Database of Systematic Reviews Issue 8 of 12, August 2024	2
Embase	12/08/24	Ovid	Embase <1974 to 2024 August 09>	771
Epistemonikos	12/08/24	Epistemonikos	n/a	75 (2 searches)
MEDLINE ALL	12/08/24	Ovid	Ovid MEDLINE(R) ALL <1946 to August 09, 2024>	364

Search strategy history

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

Searches		
#1	MeSH descriptor: [Breast Neoplasms] explode all trees	20356
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees	1014
#3	MeSH descriptor: [Carcinoma, Lobular] this term only	219
#4	MeSH descriptor: [Carcinoma, Medullary] this term only	21
#5	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only	309
#6	{OR #1-#5}	20664
#7	MeSH descriptor: [Breast] explode all trees	1156
#8	breast*:ti,ab	62451
#9	#7 or #8	62560
#10	(breast NEXT milk):ti,ab	2799
#11	(breast NEXT tender*):ti,ab	272

Searches		
#12	#10 or #11	3070
#13	#9 not #12	59490
#14	MeSH descriptor: [Neoplasms] explode all trees	125865
#15	#13 and #14	20696
#16	(breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab	44657
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab	291
#18	{OR #15-#17}	45692
#19	#6 or #18	47119
#20	MeSH descriptor: [Ovariectomy] explode all trees	419
#21	(ovariectom* or oophorectom*):ti,ab	2115
#22	(remov* near/3 ovar*):ti,ab	154
#23	((radiation or irradiation or radiotherap*) near/3 ovar*)	167
#24	MeSH descriptor: [Ovary] explode all trees	1513
#25	MeSH descriptor: [Radiation] explode all trees	8211
#26	MeSH descriptor: [Radiotherapy] explode all trees	10074
#27	#25 or #26	16727
#28	#24 and #27	7
#29	(ovar* near/3 suppress*):ti,ab	590
#30	#20 or #21 or #22 or #23 or #28 or #29	3038
#31	MeSH descriptor: [Luteinizing Hormone] explode all trees	2000
#32	(lutein* next hormon* next releas*):ti,ab	586
#33	(LHRH* or LH-RH*):ti,ab	1135
#34	MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees	3334
#35	(gonado* next releas* next hormon*):ti,ab	2489
#36	(GnRH* or GnRHA*):ti,ab	4728
#37	(goserelin* or zolade*):ti,ab	1066
#38	(buserelin* or suprefact* or suprecur*):ti,ab	391
#39	(leuprolid* or leuprorelin* or lupron* or prostap*):ti,ab	1207
#40	(nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl*):ti,ab	144
#41	(triptorelin* or decapeptyl* or gonapeptyl*):ti,ab	739
#42	(hormon* near/3 (suppress* or ablat*)):ti,ab	562
#43	{OR #31-#42}	10201
#44	#30 or #43	12803
#45	#19 and #44	1447
#46	MeSH descriptor: [Tamoxifen] explode all trees	2976
#47	(tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox*):ti,ab	4991
#48	#46 or #47	5953
#49	MeSH descriptor: [Aromatase Inhibitors] explode all trees	949
#50	(aromatase near/2 (inhibit* or block*)):ti,ab	2607
#51	(exemestane* or aromasi*):ti,ab	999

Searches	
#52	(anastrozole* or anastrazole* or arimidex*):ti,ab 1367
#53	(letrozole* or femar*):ti,ab 2606
#54	{OR #49-#53} 5502
#55	#45 and #48 619
#56	#45 and #54 575
#57	#55 or #56 in Cochrane Reviews, Cochrane Protocols 2

1 **Database name: Cochrane Database of Systematic Reviews (CDSR)**

Searches	
#1	MeSH descriptor: [Breast Neoplasms] explode all trees 20356
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees 1014
#3	MeSH descriptor: [Carcinoma, Lobular] this term only 219
#4	MeSH descriptor: [Carcinoma, Medullary] this term only 21
#5	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 309
#6	{OR #1-#5} 20664
#7	MeSH descriptor: [Breast] explode all trees 1156
#8	breast*:ti,ab 62451
#9	#7 or #8 62560
#10	(breast NEXT milk):ti,ab 2799
#11	(breast NEXT tender*):ti,ab 272
#12	#10 or #11 3070
#13	#9 not #12 59490
#14	MeSH descriptor: [Neoplasms] explode all trees 125865
#15	#13 and #14 20696
#16	(breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 44657
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 291
#18	{OR #15-#17} 45692
#19	#6 or #18 47119
#20	MeSH descriptor: [Ovariectomy] explode all trees 419
#21	(ovariectom* or oophorectom*):ti,ab 2115
#22	(remov* near/3 ovar*):ti,ab 154
#23	((radiation or irradiation or radiotherap*) near/3 ovar*) 167
#24	MeSH descriptor: [Ovary] explode all trees 1513
#25	MeSH descriptor: [Radiation] explode all trees 8211
#26	MeSH descriptor: [Radiotherapy] explode all trees 10074
#27	#25 or #26 16727
#28	#24 and #27 7
#29	(ovar* near/3 suppress*):ti,ab 590
#30	#20 or #21 or #22 or #23 or #28 or #29 3038

Searches	
#31	MeSH descriptor: [Luteinizing Hormone] explode all trees 2000
#32	(lutein* next hormon* next releas*):ti,ab 586
#33	(LHRH* or LH-RH*):ti,ab 1135
#34	MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees 3334
#35	(gonado* next releas* next hormon*):ti,ab 2489
#36	(GnRH* or GnRHA*):ti,ab 4728
#37	(goserelin* or zolade*):ti,ab 1066
#38	(buserelin* or suprefact* or suprecur*):ti,ab 391
#39	(leuprolid* or leuprorelin* or lupron* or prostap*):ti,ab 1207
#40	(nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl*):ti,ab 144
#41	(triptorelin* or decapeptyl* or gonapeptyl*):ti,ab 739
#42	(hormon* near/3 (suppress* or ablat*)):ti,ab 562
#43	{OR #31-#42} 10201
#44	#30 or #43 12803
#45	#19 and #44 1447
#46	MeSH descriptor: [Tamoxifen] explode all trees 2976
#47	(tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox*):ti,ab 4991
#48	#46 or #47 5953
#49	MeSH descriptor: [Aromatase Inhibitors] explode all trees 949
#50	(aromatase near/2 (inhibit* or block*)):ti,ab 2607
#51	(exemestane* or aromasi*):ti,ab 999
#52	(anastrozole* or anastrazole* or arimidex*):ti,ab 1367
#53	(letrozole* or femar*):ti,ab 2606
#54	{OR #49-#53} 5502
#55	#45 and #48 619
#56	#45 and #54 575
#57	#55 or #56 in Cochrane Reviews, Cochrane Protocols 2
#58	#55 or #56 in Trials 876
#59	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 527901
#60	"conference":pt 246591
#61	#59 or #60 774492
#62	#58 not #61 372

1 **Database name: Embase**

Searches	
1	exp breast cancer/ 606659
2	exp breast carcinoma/ 100713
3	exp medullary carcinoma/ 13160

Searches
4 ductal breast carcinoma in situ/ 3543
5 exp breast tumor/ 689624
6 lobular carcinoma/ 3621
7 or/1-6 701203
8 exp breast/ 130603
9 breast*.ti,ab,kw. 816012
10 8 or 9 849251
11 (breast adj milk).ti,ab,kw. 20940
12 (breast adj tender*).ti,ab,kw. 787
13 11 or 12 21721
14 10 not 13 827530
15 exp neoplasm/ 5828287
16 14 and 15 630312
17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 629236
18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 44514
19 16 or 17 or 18 706535
20 7 or 19 834853
21 *ovariectomy/ 10870
22 (ovariectom* or oophorectom*).ti,ab. 54886
23 (remov* adj3 ovar*).ti,ab. 3656
24 ((radiation or irradiation or radiotherap*) adj3 ovar*).ti,ab. 1024
25 *ovary/ 19547
26 *radiation/ 15167
27 *radiotherapy/ or *cancer radiotherapy/ 119999
28 26 or 27 133912
29 25 and 28 103
30 (ovar* adj3 suppress*).ti,ab. 4150
31 or/21-24,29-30 64089
32 *luteinizing hormone/ 24815
33 exp gonadorelin derivative/ 84851
34 (lutein* adj hormon* adj releas*).ti,ab. 7609
35 (LHRH* or LH-RH*).ti,ab. 12845
36 exp growth hormone releasing factor derivative/ 10327
37 (gonado* adj releas* adj hormon*).ti,ab. 23432
38 (GnRH* or GnRHA*).ti,ab. 35909
39 (goserelin* or zolade* or "ici 118630*" or ici118630* or "ly 01005*" or ly01005* or novimp* or prozoladex* or reseligo* or "zd 9393*" or zd9393* or zoreline*).ti,ab. 2163
40 (buserelin* or suprefact* or suprecur* or "hoe 706*" or hoe706* or "hoe 766*" or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*).ti,ab. 2606

Searches
41 (leuprolid* or leuprorelin* or lupron* or prostap* or a 43818* or a43818* or "abbott 43818*" or abbott43818* or "cam 2032*" or cam2032* or camcevi* or carcinil* or "ckd 841*" or ckd841* or daronda* or "depo lupron*" or eligard* or eliprogel* or elityran* or elityran depot* or enanton* or enantone* or fensolvi* or "fp 001*" or fp001* or ginecrin* or klebrocid* or "la 2575*" or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or "nh 901*" or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or "sot 375*" or sot375* or staladex* or "tap 144*" or tap144* or tapros* or "tol 2506*" or tol2506* or trenantone* or viadur* or "vp 4896*" or Vp4896* or zeulide*).ti,ab. 4957
42 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or "rs 94991*" or rs94991* or rsynarel* or synrelin*).ti,ab. 784
43 (triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or "ay 25650*" or ay25650* or "bim 21003*" or bim21003* or "bn 52014*" or Bn52014* or "cl 118532*" or cl118532* or "debio 8200*" or "debio 8206*" or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or "isr 048*" or isr 48* or isr048* or isr48* or "ly 01007*" or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or "wy 42422*" or "wy 42462*" or wy42422* or wy42462*).ti,ab. 1898
44 (hormon* adj3 (suppress* or ablat*)).ti,ab. 6801
45 or/32-44 128593
46 31 or 45 186388
47 20 and 46 13926
48 *tamoxifen/ 19719
49 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or "ici 47699*" or ici47699 or tomaxithen* or zitazonium* or ebefen* or kessar* or "nsc 180973*" or nsc180973 or "pt 101*" or pt101 or tamoplac* or tamoxasta*).ti,ab. 40488
50 48 or 49 45031
51 aromatase inhibitor/ or *exemestane/ or *anastrozole/ or *letrozole/ 23158
52 (aromatase adj2 (inhibit* or block*)).ti,ab. 16113
53 (exemestane* or aromasi* or "fce 24304*" or fce24304* or nakides* or nikidess* or "pnu 155971*" or pnu15597*).ti,ab. 3018
54 (anastrozole* or anastrazole* or arimidex* or "ici d1033*" or icid1033* or "zd 1033*" or zd1033* or zeneca* or femathina* or "mpi 674*" or "mpi 676*" or mpi674* or mpi676* or trozolet*).ti,ab. 7074
55 (letrozole* or femar* or "cgs 20267*" or cgs20267* or loxifan*).ti,ab. 7990
56 or/51-55 33916
57 47 and 50 2737
58 47 and 56 3346
59 57 or 58 4739
60 exp Randomized Controlled Trial/ 841475
61 randomi?ed.mp. 1584252
62 placebo.mp. 543063
63 or/60-62 1823424
64 59 and 63 1231
65 limit 64 to english language 1180
66 nonhuman/ not human/ 5511060
67 65 not 66 1164

Searches		
68	(conference abstract* or conference review or conference paper or conference proceeding or editorial or letter).db,pt,su.	8160254
69	67 not 68	774
70	case report/	3032176
71	69 not 70	771

Database name: Epistimonikos – Search 1 (Breast cancer AND Ovarian suppression AND Tamoxifen)

Searches
(title:((title:((breast* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*))) OR abstract:((breast* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)))) AND (title:((ovariectom* OR oophorectom*) OR (remov* AND ovar*) OR ((radiation OR irradiation OR radiotherap*) AND ovar*) OR (ovar* AND suppress*) OR (lutein* AND hormon* AND releas*) OR (lhrh* OR lh-rh*) OR (gonado* AND releas* AND hormon*) OR (gnrh* OR gnrha*) OR (goserelin* OR zolade*) OR (buserelin* OR suprefact* OR suprecur*) OR (leuprolid* OR leuprorelin* OR lupron* OR prostap*) OR (nafarelin* OR synarel* OR gonadorelin* OR napharelin* OR nasanyl*) OR (triptorelin* OR decapeptyl* OR gonapeptyl*) OR (hormon* AND (suppress* OR ablat*))) OR abstract:((ovariectom* OR oophorectom*) OR (remov* AND ovar*) OR ((radiation OR irradiation OR radiotherap*) AND ovar*) OR (ovar* AND suppress*) OR (lutein* AND hormon* AND releas*) OR (lhrh* OR lh-rh*) OR (gonado* AND releas* AND hormon*) OR (gnrh* OR gnrha*) OR (goserelin* OR zolade*) OR (buserelin* OR suprefact* OR suprecur*) OR (leuprolid* OR leuprorelin* OR lupron* OR prostap*) OR (nafarelin* OR synarel* OR gonadorelin* OR napharelin* OR nasanyl*) OR (triptorelin* OR decapeptyl* OR gonapeptyl*) OR (hormon* AND (suppress* OR ablat*)))) AND (title:((tamoxifen* OR tamofen* OR tamone* OR nolvadex* OR soltamox*)) OR abstract:((tamoxifen* OR tamofen* OR tamone* OR nolvadex* OR soltamox*)))) OR abstract:((title:((breast* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*))) OR abstract:((breast* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)))) AND (title:((ovariectom* OR oophorectom*) OR (remov* AND ovar*) OR ((radiation OR irradiation OR radiotherap*) AND ovar*) OR (ovar* AND suppress*) OR (lutein* AND hormon* AND releas*) OR (lhrh* OR lh-rh*) OR (gonado* AND releas* AND hormon*) OR (gnrh* OR gnrha*) OR (goserelin* OR zolade*) OR (buserelin* OR suprefact* OR suprecur*) OR (leuprolid* OR leuprorelin* OR lupron* OR prostap*) OR (nafarelin* OR synarel* OR gonadorelin* OR napharelin* OR nasanyl*) OR (triptorelin* OR decapeptyl* OR gonapeptyl*) OR (hormon* AND (suppress* OR ablat*))) OR abstract:((ovariectom* OR

Searches
oophorectom*) OR (remov* AND ovar*) OR ((radiation OR irradiation OR radiotherap*) AND ovar*) OR (ovar* AND suppress*) OR (lutein* AND hormon* AND releas*) OR (lhrh* OR lh-rh*) OR (gonado* AND releas* AND hormon*) OR (gnrh* OR gnrha*) OR (goserelin* OR zolade*) OR (buserelin* OR suprefact* OR suprecur*) OR (leuprolid* OR leuprorelin* OR lupron* OR prostap*) OR (nafarelin* OR synarel* OR gonadorelin* OR napharelin* OR nasanyl*) OR (triptorelin* OR decapeptyl* OR gonapeptyl*) OR (hormon* AND (suppress* OR ablat*)))) AND (title:((tamoxifen* OR tamofen* OR tamone* OR nolvadex* OR soltamox*)) OR abstract:((tamoxifen* OR tamofen* OR tamone* OR nolvadex* OR soltamox*))))) [Filters: classification=systematic-review]

Database name: Epistimonikos – Search 2 (Breast cancer AND Ovarian suppression AND Aromatase Inhibitors)

Searches
(title:((title:((breast* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*))) OR abstract:((breast* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)))) AND (title:((ovariectom* OR oophorectom*) OR (remov* AND ovar*) OR ((radiation OR irradiation OR radiotherap*) AND ovar*) OR (ovar* AND suppress*) OR (lutein* AND hormon* AND releas*) OR (lhrh* OR lh-rh*) OR (gonado* AND releas* AND hormon*) OR (gnrh* OR gnrha*) OR (goserelin* OR zolade*) OR (buserelin* OR suprefact* OR suprecur*) OR (leuprolid* OR leuprorelin* OR lupron* OR prostap*) OR (nafarelin* OR synarel* OR gonadorelin* OR napharelin* OR nasanyl*) OR (triptorelin* OR decapeptyl* OR gonapeptyl*) OR (hormon* AND (suppress* OR ablat*))) OR abstract:((ovariectom* OR oophorectom*) OR (remov* AND ovar*) OR ((radiation OR irradiation OR radiotherap*) AND ovar*) OR (ovar* AND suppress*) OR (lutein* AND hormon* AND releas*) OR (lhrh* OR lh-rh*) OR (gonado* AND releas* AND hormon*) OR (gnrh* OR gnrha*) OR (goserelin* OR zolade*) OR (buserelin* OR suprefact* OR suprecur*) OR (leuprolid* OR leuprorelin* OR lupron* OR prostap*) OR (nafarelin* OR synarel* OR gonadorelin* OR napharelin* OR nasanyl*) OR (triptorelin* OR decapeptyl* OR gonapeptyl*) OR (hormon* AND (suppress* OR ablat*)))) AND (title:((aromatase AND (inhibit* OR block*)) OR (exemestane* OR aromasi*) OR (anastrozole* OR anastrazole* OR arimidex*) OR (letrozole* OR femar*)) OR abstract:((aromatase AND (inhibit* OR block*)) OR (exemestane* OR aromasi*) OR (anastrozole* OR anastrazole* OR arimidex*) OR (letrozole* OR femar*)))) OR abstract:((title:((breast* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*))) OR abstract:((breast* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumour* OR tumor* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular

Searches
OR malignan*)))) AND (title:((ovariectom* OR oophorectom*) OR (remov* AND ovar*) OR ((radiation OR irradiation OR radiotherap*) AND ovar*) OR (ovar* AND suppress*) OR (lutein* AND hormon* AND releas*) OR (lhrh* OR lh-rh*) OR (gonado* AND releas* AND hormon*) OR (gnrh* OR gnrha*) OR (goserelin* OR zolade*) OR (buserelin* OR suprefact* OR suprecur*) OR (leuprolid* OR leuprorelin* OR lupron* OR prostap*) OR (nafarelin* OR synarel* OR gonadorelin* OR napharelin* OR nasanyl*) OR (triptorelin* OR decapeptyl* OR gonapeptyl*) OR (hormon* AND (suppress* OR ablat*))) OR abstract:((ovariectom* OR oophorectom*) OR (remov* AND ovar*) OR ((radiation OR irradiation OR radiotherap*) AND ovar*) OR (ovar* AND suppress*) OR (lutein* AND hormon* AND releas*) OR (lhrh* OR lh-rh*) OR (gonado* AND releas* AND hormon*) OR (gnrh* OR gnrha*) OR (goserelin* OR zolade*) OR (buserelin* OR suprefact* OR suprecur*) OR (leuprolid* OR leuprorelin* OR lupron* OR prostap*) OR (nafarelin* OR synarel* OR gonadorelin* OR napharelin* OR nasanyl*) OR (triptorelin* OR decapeptyl* OR gonapeptyl*) OR (hormon* AND (suppress* OR ablat*)))) AND (title:((aromatase AND (inhibit* OR block*)) OR (exemestane* OR aromasi*) OR (anastrozole* OR anastrazole* OR arimidex*) OR (letrozole* OR femar*)) OR abstract:((aromatase AND (inhibit* OR block*)) OR (exemestane* OR aromasi*) OR (anastrozole* OR anastrazole* OR arimidex*) OR (letrozole* OR femar*))))) [Filters: classification=systematic-review]

1

2 **Database name: Medline ALL**

Searches		
1	exp Breast Neoplasms/	357009
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/	48537
3	Carcinoma, Lobular/	6185
4	Carcinoma, Medullary/	3425
5	Carcinoma, Intraductal, Noninfiltrating/	10896
6	or/1-5	377530
7	exp Breast/	54935
8	breast*.ti,ab,kw.	587352
9	7 or 8	597367
10	(breast adj milk).ti,ab,kw.	16430
11	(breast adj tender*).ti,ab,kw.	599
12	10 or 11	17026
13	9 not 12	580341
14	exp Neoplasms/	4004629
15	13 and 14	375027
16	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw.	436882
17	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw.	37289
18	or/15-17	493796
19	6 or 18	551996
20	exp Ovariectomy/	27791

Searches	
21	(ovariectom* or oophorectom*).ti,ab. 42875
22	(remov* adj3 ovar*).ti,ab. 2543
23	((radiation or irradiation or radiotherap*) adj3 ovar*).ti,ab. 808
24	exp Ovary/ 99175
25	exp Radiation/ 533218
26	exp Radiotherapy/ 212974
27	25 or 26 704668
28	24 and 27 2268
29	(ovar* adj3 suppress*).ti,ab. 2962
30	or/20-23,28-29 57004
31	exp Luteinizing Hormone/ 48579
32	(lutein* adj hormon* adj releas*).ti,ab. 6939
33	(LHRH* or LH-RH*).ti,ab. 9941
34	exp Gonadotropin-Releasing Hormone/ 34977
35	(gonado* adj releas* adj hormon*).ti,ab. 19892
36	(GnRH* or GnRHA*).ti,ab. 26384
37	(goserelin* or zolade* or "ici 118630*" or ici118630* or "ly 01005*" or ly01005* or novimp* or prozoladex* or reseligo* or "zd 9393*" or zd9393* or zoreline*).ti,ab. 1364
38	(buserelin* or suprefact* or suprecur* or "hoe 706*" or hoe706* or "hoe 766*" or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*).ti,ab. 2181
39	(leuprolid* or leuprorelin* or lupron* or prostap* or a 43818* or a43818* or "abbott 43818*" or abbott43818* or "cam 2032*" or cam2032* or camcevi* or carcinil* or "ckd 841*" or ckd841* or daronda* or "depo lupron*" or eligard* or eliprogel* or elityran* or elityran depot* or enanton* or enantone* or fensolvi* or "fp 001*" or fp001* or ginecrin* or klebrocid* or "la 2575*" or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or "nh 901*" or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or "sot 375*" or sot375* or staladex* or "tap 144*" or tap144* or tapros* or "tol 2506*" or tol2506* or trenantone* or viadur* or "vp 4896*" or Vp4896* or zeulide*).ti,ab. 2993
40	(nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or "rs 94991*" or rs94991* or rsynarel* or synrelin*).ti,ab. 545
41	(triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or "ay 25650*" or ay25650* or "bim 21003*" or bim21003* or "bn 52014*" or Bn52014* or "cl 118532*" or cl118532* or "debio 8200*" or "debio 8206*" or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or "isr 048*" or isr 48* or isr048* or isr48* or "ly 01007*" or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or "wy 42422*" or "wy 42462*" or wy42422* or wy42462*).ti,ab. 1138
42	(hormon* adj3 (suppress* or ablat*)).ti,ab. 5254
43	or/31-42 91217
44	30 or 43 142161
45	19 and 44 6809
46	exp Tamoxifen/ 23046
47	(tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or "ici 47699*" or ici47699 or tomaxithen* or zitazonium* or ebefen* or kessar* or "nsc 180973*" or nsc180973 or "pt 101*" or pt101 or tamoplac* or tamoxasta*).ti,ab. 26015

Searches		
48	46 or 47	33196
49	exp Aromatase Inhibitors/	10298
50	(aromatase adj2 (inhibit* or block*)).ti,ab.	9709
51	(exemestane* or aromasi* or "fce 24304*" or fce24304* or nakides* or nikidess* or "pnu 155971*" or pnu15597*).ti,ab.	1553
52	(anastrozole* or anastrazole* or arimidex* or "ici d1033*" or icid1033* or "zd 1033*" or zd1033* or zeneca* or femathina* or "mpi 674*" or "mpi 676*" or mpi674* or mpi676* or trozolet*).ti,ab.	2588
53	(letrozole* or femar* or "cgs 20267*" or cgs20267* or loxifan*).ti,ab.	4138
54	or/49-53	16145
55	45 and 48	1669
56	45 and 54	1023
57	55 or 56	2098
58	exp Randomized Controlled Trial/	620339
59	randomi?ed.mp.	1134657
60	placebo.mp.	258896
61	or/58-60	1202863
62	57 and 61	426
63	limit 62 to english language	390
64	Animals/ not (Animals/ and Humans/)	5213376
65	63 not 64	380
66	limit 65 to (case reports or clinical conference or comment or consensus development conference or consensus development conference, nih or editorial or letter)	16
67	65 not 66	364

1 **Cost-effectiveness searches**

Database results

2

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	15/08/24	Ovid	Embase <1974 to 2024 August 14>	105
Econlit	15/08/24	Ovid	Econlit <1886 to August 1, 2024>	6
INAHTA	15/08/24	INAHTA		11
Medline ALL	15/08/24	Ovid	Ovid MEDLINE(R) ALL <1946 to August 14, 2024>	33
NHS EED	15/08/24	CRD		2

1 Search strategy history

2 Database name: Embase

Searches	
1	exp breast cancer/ 607022
2	exp breast carcinoma/ 100738
3	exp medullary carcinoma/ 13168
4	ductal breast carcinoma in situ/ 3550
5	exp breast tumor/ 690013
6	lobular carcinoma/ 3622
7	or/1-6 701600
8	exp breast/ 130634
9	breast*.ti,ab,kw. 816537
10	8 or 9 849783
11	(breast adj milk).ti,ab,kw. 20954
12	(breast adj tender*).ti,ab,kw. 787
13	11 or 12 21735
14	10 not 13 828048
15	exp neoplasm/ 5832039
16	14 and 15 630728
17	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 629650
18	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 44524
19	16 or 17 or 18 706965
20	7 or 19 835293
21	*ovariectomy/ 10870
22	(ovariectom* or oophorectom*).ti,ab. 54900
23	(remov* adj3 ovar*).ti,ab. 3656
24	((radiation or irradiation or radiotherap*) adj3 ovar*).ti,ab. 1024
25	*ovary/ 19574
26	*radiation/ 15170
27	*radiotherapy/ or *cancer radiotherapy/ 120003
28	26 or 27 133919
29	25 and 28 103
30	(ovar* adj3 suppress*).ti,ab. 4151
31	or/21-24,29-30 64104
32	*luteinizing hormone/ 24816
33	exp gonadorelin derivative/ 84869
34	(lutein* adj hormon* adj releas*).ti,ab. 7609
35	(LHRH* or LH-RH*).ti,ab. 12845
36	exp growth hormone releasing factor derivative/ 10332

Searches
37 (gonado* adj releas* adj hormon*).ti,ab. 23442
38 (GnRH* or GnRHA*).ti,ab. 35923
39 (goserelin* or zolade* or "ici 118630*" or ici118630* or "ly 01005*" or ly01005* or novimp* or prozoladex* or reseligo* or "zd 9393*" or zd9393* or zoreline*).ti,ab. 2164
40 (buserelin* or suprefact* or suprecur* or "hoe 706*" or hoe706* or "hoe 766*" or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*).ti,ab. 2606
41 (leuprolid* or leuprorelin* or lupron* or prostap* or a 43818* or a43818* or "abbott 43818*" or abbott43818* or "cam 2032*" or cam2032* or camcevi* or carcinil* or "ckd 841*" or ckd841* or daronda* or "depo lupron*" or eligard* or eliprogel* or elityran* or elityran depot* or enanton* or enantone* or fensolvi* or "fp 001*" or fp001* or ginecrin* or klebrocid* or "la 2575*" or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or "nh 901*" or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or "sot 375*" or sot375* or staladex* or "tap 144*" or tap144* or tapros* or "tol 2506*" or tol2506* or trenantone* or viadur* or "vp 4896*" or Vp4896* or zeulide*).ti,ab. 4958
42 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or "rs 94991*" or rs94991* or rsynarel* or synrelin*).ti,ab. 784
43 (triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or "ay 25650*" or ay25650* or "bim 21003*" or bim21003* or "bn 52014*" or Bn52014* or "cl 118532*" or cl118532* or "debio 8200*" or "debio 8206*" or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or "isr 048*" or isr 48* or isr048* or isr48* or "ly 01007*" or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or "wy 42422*" or "wy 42462*" or wy42422* or wy42462*).ti,ab. 1898
44 (hormon* adj3 (suppress* or ablat*)).ti,ab. 6804
45 or/32-44 128623
46 31 or 45 186433
47 20 and 46 13926
48 *tamoxifen/ 19725
49 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or "ici 47699*" or ici47699 or tomaxithen* or zitazonium* or ebefen* or kessar* or "nsc 180973*" or nsc180973 or "pt 101*" or pt101 or tamoplac* or tamoxasta*).ti,ab. 40501
50 48 or 49 45045
51 aromatase inhibitor/ or *exemestane/ or *anastrozole/ or *letrozole/ 23169
52 (aromatase adj2 (inhibit* or block*)).ti,ab. 16115
53 (exemestane* or aromasi* or "fce 24304*" or fce24304* or nakides* or nikidess* or "pnu 155971*" or pnu15597*).ti,ab. 3020
54 (anastrozole* or anastrazole* or arimidex* or "ici d1033*" or icid1033* or "zd 1033*" or zd1033* or zeneca* or femathina* or "mpi 674*" or "mpi 676*" or mpi674* or mpi676* or trozolet*).ti,ab. 7075
55 (letrozole* or femar* or "cgs 20267*" or cgs20267* or loxifan*).ti,ab. 7996
56 or/51-55 33929
57 47 and 50 2737
58 47 and 56 3346
59 57 or 58 4739
60 exp Health Economics/ 1089694

Searches	
61	exp "Health Care Cost"/ 357166
62	exp Pharmacoeconomics/ 245722
63	Monte Carlo Method/ 54556
64	Decision Tree/ 25576
65	econom$.tw. 536105
66	cba.tw. 14663
67	cea.tw. 43601
68	cua.tw. 1994
69	markov$.tw. 42597
70	(monte adj carlo).tw. 65108
71	(decision adj3 (tree$ or analys$)).tw. 44160
72	(cost or costs or costing$ or costly or costed).tw. 1066042
73	(price$ or pricing$).tw. 78135
74	budget$.tw. 50101
75	expenditure$.tw. 95908
76	(value adj3 (money or monetary)).tw. 4570
77	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. 9980
78	or/60-77 2405227
79	59 and 78 272
80	limit 79 to english language 265
81	limit 80 to dc=20100101-20240816 159
82	nonhuman/ not human/ 5514339
83	81 not 82 159
84	(conference abstract* or conference review or conference paper or conference proceeding or editorial or letter).db,pt,su. 8163892
85	case report/ 3033597
86	84 or 85 10558385
87	83 not 86 105

1 **Database name: Econlit**

Searches	
1	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 408
2	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 1
3	or/1-2 409
4	(ovariectom* or oophorectom*).ti,ab,kw. 8
5	(remov* adj3 ovar*).ti,ab,kw. 0
6	((radiation or irradiation or radiotherap*) adj3 ovar*).ti,ab,kw. 0
7	(ovar* adj3 suppress*).ti,ab,kw. 0
8	or/4-7 8
9	(lutein* adj hormon* adj releas*).ti,ab,kw. 1

Searches
10 (LHRH* or LH-RH*).ti,ab,kw. 0
11 (gonado* adj releas* adj hormon*).ti,ab,kw. 0
12 (GnRH* or GnRHA*).ti,ab,kw. 0
13 (goserelin* or zolade* or "ici 118630*" or ici118630* or "ly 01005*" or ly01005* or novimp* or prozoladex* or reseligo* or "zd 9393*" or zd9393* or zoreline*).ti,ab,kw. 0
14 (buserelin* or suprefact* or suprecur* or "hoe 706*" or hoe706* or "hoe 766*" or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*).ti,ab,kw. 3
15 (leuprolid* or leuprorelin* or lupron* or prostap* or a 43818* or a43818* or "abbott 43818*" or abbott43818* or "cam 2032*" or cam2032* or camcevi* or carcinil* or "ckd 841*" or ckd841* or daronda* or "depo lupron*" or eligard* or eliprogel* or elityran* or elityran depot* or enanton* or enantone* or fensolvi* or "fp 001*" or fp001* or ginecrin* or klebrocid* or "la 2575*" or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or "nh 901*" or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or "sot 375*" or sot375* or staladex* or "tap 144*" or tap144* or tapros* or "tol 2506*" or tol2506* or trenantone* or viadur* or "vp 4896*" or Vp4896* or zeulide*).ti,ab,kw. 1
16 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or "rs 94991*" or rs94991* or rsynarel* or synrelin*).ti,ab,kw. 0
17 (triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or "ay 25650*" or ay25650* or "bim 21003*" or bim21003* or "bn 52014*" or Bn52014* or "cl 118532*" or cl118532* or "debio 8200*" or "debio 8206*" or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or "isr 048*" or isr 48* or isr048* or isr48* or "ly 01007*" or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or "wy 42422*" or "wy 42462*" or wy42422* or wy42462*).ti,ab,kw. 0
18 (hormon* adj3 (suppress* or ablat*)).ti,ab,kw. 1
19 or/9-18 6
20 8 or 19 14
21 3 and 20 7
22 limit 21 to yr="2010 -Current" 6

1 **Database name: INAHTA**

Searches
(((hormon*) AND (suppress* or ablat*)) OR ((goserelin* or zolade* or buserelin* or suprefact* or triptorelin* or decapeptyl* or gonapeptyl* or nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or leuprolid* or leuprorelin* or lupron* or prostap* or suprecur* or)) OR ((GnRH*) OR (GnRHA*)) OR ((gonado*) AND (releas*) AND (hormon*)) OR ((LHRH*) OR (LH-RH*)) OR ((lutein*) AND (hormon*) AND (releas*)) OR ((ovar*) AND (suppress*)) OR ((radiation or irradiation or radiotherap*) AND (ovar*)) OR ((remov*) AND (ovar*)) OR ((Ovariectomy)[mhe] OR (Luteinizing Hormone)[mhe] OR (Gonadotropin-Releasing Hormone])[mhe])) AND (((((((mammar* AND (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))) OR ((breast* AND (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))) OR ("Carcinoma, Intraductal, Noninfiltrating"[mh]) OR ("Carcinoma, Medullary"[mh]) OR ("Carcinoma, Lobular"[mh]) OR ("Neoplasms, Ductal, Lobular, and Medullary"[mhe]) OR ("Breast Neoplasms"[mhe]))))))))

Searches
Filter by year 2010 to 2024

Database name: MEDLINE ALL

Searches	
1	exp Breast Neoplasms/ 357147
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/ 48554
3	Carcinoma, Lobular/ 6185
4	Carcinoma, Medullary/ 3427
5	Carcinoma, Intraductal, Noninfiltrating/ 10898
6	or/1-5 377682
7	exp Breast/ 54932
8	breast*.ti,ab,kw. 587778
9	7 or 8 597792
10	(breast adj milk).ti,ab,kw. 16444
11	(breast adj tender*).ti,ab,kw. 599
12	10 or 11 17040
13	9 not 12 580752
14	exp Neoplasms/ 4006024
15	13 and 14 375207
16	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 437216
17	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 37300
18	or/15-17 494145
19	6 or 18 552361
20	exp Ovariectomy/ 27795
21	(ovariectom* or oophorectom*).ti,ab. 42884
22	(remov* adj3 ovar*).ti,ab. 2544
23	((radiation or irradiation or radiotherap*) adj3 ovar*).ti,ab. 809
24	exp Ovary/ 99189
25	exp Radiation/ 533362
26	exp Radiotherapy/ 213019
27	25 or 26 704847
28	24 and 27 2268
29	(ovar* adj3 suppress*).ti,ab. 2967
30	or/20-23,28-29 57020
31	exp Luteinizing Hormone/ 48581
32	(lutein* adj hormon* adj releas*).ti,ab. 6939
33	(LHRH* or LH-RH*).ti,ab. 9942
34	exp Gonadotropin-Releasing Hormone/ 34983
35	(gonado* adj releas* adj hormon*).ti,ab. 19893

Searches
36 (GnRH* or GnRHA*).ti,ab. 26385
37 (goserelin* or zolade* or "ici 118630*" or ici118630* or "ly 01005*" or ly01005* or novimp* or prozoladex* or reseligo* or "zd 9393*" or zd9393* or zoreline*).ti,ab. 1367
38 (buserelin* or suprefact* or suprecur* or "hoe 706*" or hoe706* or "hoe 766*" or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*).ti,ab. 2181
39 (leuprolid* or leuprorelin* or lupron* or prostap* or a 43818* or a43818* or "abbott 43818*" or abbott43818* or "cam 2032*" or cam2032* or camcevi* or carcinil* or "ckd 841*" or ckd841* or daronda* or "depo lupron*" or eligard* or eliprogel* or elityran* or elityran depot* or enanton* or enantone* or fensolvi* or "fp 001*" or fp001* or ginecrin* or klebrocid* or "la 2575*" or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or "nh 901*" or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or "sot 375*" or sot375* or staladex* or "tap 144*" or tap144* or tapros* or "tol 2506*" or tol2506* or trenantone* or viadur* or "vp 4896*" or Vp4896* or zeulide*).ti,ab. 2995
40 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or "rs 94991*" or rs94991* or rsynarel* or synrelin*).ti,ab. 545
41 (triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or "ay 25650*" or ay25650* or "bim 21003*" or bim21003* or "bn 52014*" or Bn52014* or "cl 118532*" or cl118532* or "debio 8200*" or "debio 8206*" or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or "isr 048*" or isr 48* or isr048* or isr48* or "ly 01007*" or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or "wy 42422*" or "wy 42462*" or wy42422* or wy42462*).ti,ab. 1138
42 (hormon* adj3 (suppress* or ablat*)).ti,ab. 5255
43 or/31-42 91229
44 30 or 43 142190
45 19 and 44 6811
46 exp Tamoxifen/ 23050
47 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or "ici 47699*" or ici47699 or tomaxithen* or zitazonium* or ebefen* or kessar* or "nsc 180973*" or nsc180973 or "pt 101*" or pt101 or tamoplac* or tamoxasta*).ti,ab. 26026
48 46 or 47 33207
49 exp Aromatase Inhibitors/ 10306
50 (aromatase adj2 (inhibit* or block*)).ti,ab. 9714
51 (exemestane* or aromasi* or "fce 24304*" or fce24304* or nakides* or nikidess* or "pnu 155971*" or pnu15597*).ti,ab. 1555
52 (anastrozole* or anastrazole* or arimidex* or "ici d1033*" or icid1033* or "zd 1033*" or zd1033* or zeneca* or femathina* or "mpi 674*" or "mpi 676*" or mpi674* or mpi676* or trozolet*).ti,ab. 2591
53 (letrozole* or femar* or "cgs 20267*" or cgs20267* or loxifan*).ti,ab. 4141
54 or/49-53 16154
55 45 and 48 1669
56 45 and 54 1025
57 55 or 56 2100
58 Economics/ 27539
59 exp "Costs and Cost Analysis"/ 272390

Searches
60 Economics, Dental/ 1922
61 exp Economics, Hospital/ 25940
62 exp Economics, Medical/ 14442
63 Economics, Nursing/ 4013
64 Economics, Pharmaceutical/ 3144
65 Budgets/ 11838
66 exp Models, Economic/ 16465
67 Markov Chains/ 16360
68 Monte Carlo Method/ 33177
69 Decision Trees/ 12299
70 econom$.tw. 442234
71 cba.tw. 11442
72 cea.tw. 28171
73 cua.tw. 1514
74 markov$.tw. 33750
75 (monte adj carlo).tw. 62269
76 (decision adj3 (tree$ or analys$)).tw. 33326
77 (cost or costs or costing$ or costly or costed).tw. 802355
78 (price$ or pricing$).tw. 57262
79 budget$.tw. 37944
80 expenditure$.tw. 72485
81 (value adj3 (money or monetary)).tw. 3403
82 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 4656
83 or/58-82 1537933
84 57 and 83 59
85 limit 84 to english language 56
86 limit 85 to ed=20100101-20240816 32
87 limit 85 to dt=20100101-20240816 36
88 86 or 87 37
89 Animals/ not (Animals/ and Humans/) 5214574
90 88 not 89 37
91 limit 90 to (case reports or clinical conference or comment or consensus development conference or consensus development conference, nih or editorial or letter) 4
92 90 not 91 33

1 **Database name: NHS EED**

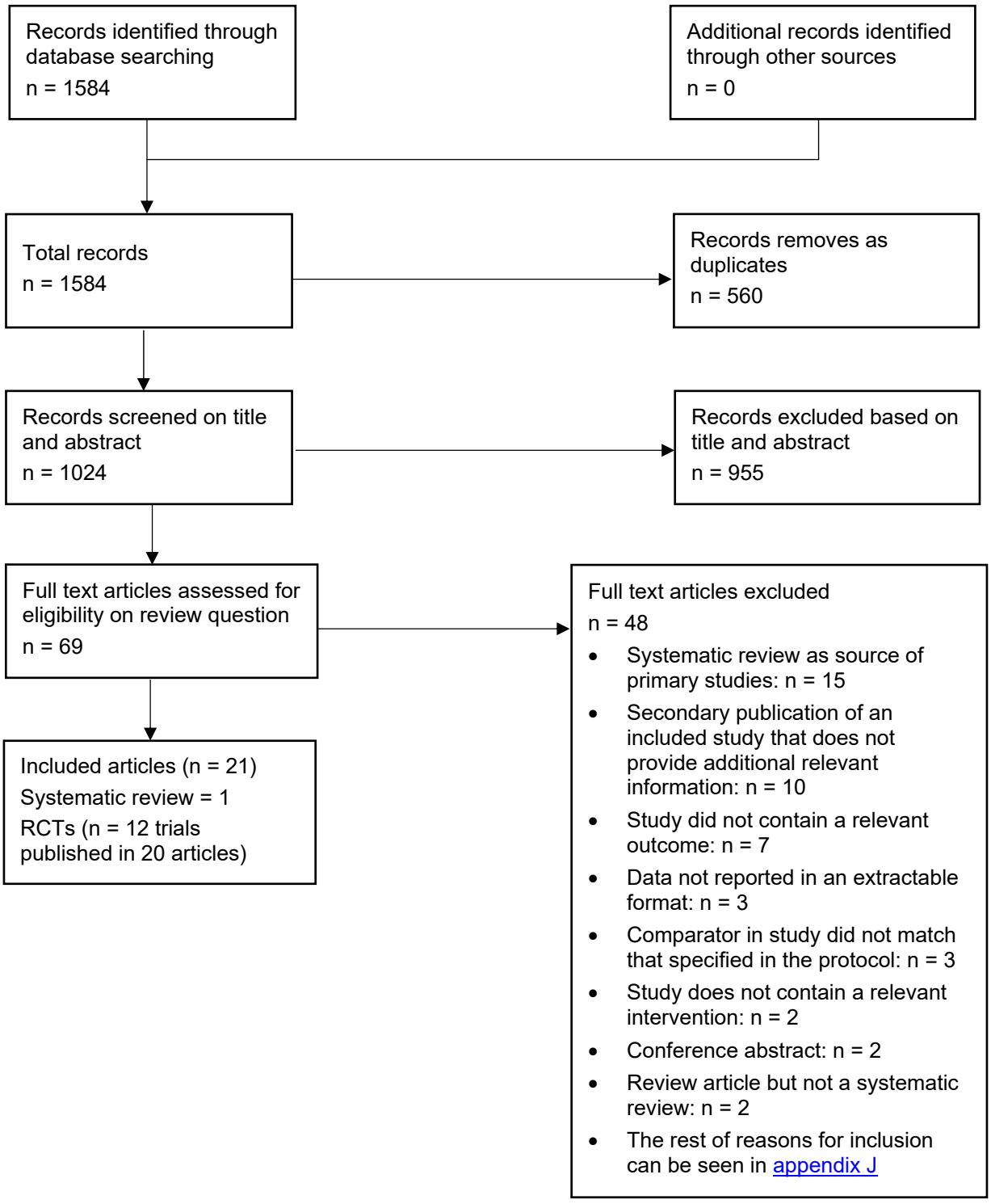
Searches
1 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
2 MESH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES
3 MESH DESCRIPTOR Carcinoma, Lobular
4 MESH DESCRIPTOR Carcinoma, Medullary
5 MESH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating

Searches
6 #1 or #2 or #3 or #4 or #5
7 MESH DESCRIPTOR Breast EXPLODE ALL TREES
8 breast*
9 #7 or #8
10 (breast NEXT milk)
11 (breast NEXT tender*)
12 #10 or #11
13 #9 not #12
14 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES
15 #13 and #14
16 (breast* NEAR5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))
17 (mammar* near5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))
18 #15 or #16 or #17
19 #6 or #18
20 MESH DESCRIPTOR Ovariectomy EXPLODE ALL TREES
21 (ovariectom* or oophorectom*)
22 (remov* near3 ovar*)
23 ((radiation or irradiation or radiotherap*) near3 ovar*)
24 MESH DESCRIPTOR Ovary EXPLODE ALL TREES
25 MESH DESCRIPTOR Radiation EXPLODE ALL TREES
26 MESH DESCRIPTOR Radiotherapy EXPLODE ALL TREES
27 #25 or #26
28 #24 and #27
29 (ovar* near3 suppress*)
30 #20 or #21 or #22 or #23 or #28 or #29
31 MESH DESCRIPTOR Luteinizing Hormone EXPLODE ALL TREES
32 (lutein* next hormon* next releas*)
33 (LHRH* or LH-RH*)
34 MESH DESCRIPTOR Gonadotropin-Releasing Hormone EXPLODE ALL TREES
35 (gonado* next releas* next hormon*)
36 (GnRH* or GnRHA*)
37 (goserelin* or zolade*)
38 (buserelin* or suprefact* or suprecur*)
39 (leuprolid* or leuprorelin* or lupron* or prostap*)
40 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl*)
41 (triptorelin* or decapeptyl* or gonapeptyl*)
42 (hormon* near3 (suppress* or ablat*))
43 #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42
44 #30 or #43
45 #19 and #44

Searches
46 MESH DESCRIPTOR Tamoxifen EXPLODE ALL TREES
47 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox*)
48 #46 or #47
49 MESH DESCRIPTOR Aromatase Inhibitors EXPLODE ALL TREES
50 (aromatase near2 (inhibit* or block*))
51 (exemestane* or aromasi*)
52 (anastrozole* or anastrazole* or arimidex*)
53 (letrozole* or femar*)
54 #49 or #50 or #51 or #52 or #53
55 #45 and #48
56 #45 and #54
57 #55 OR #56
58 (#57) IN NHSEED
59 (#58) FROM 2010 TO 2024

1

Appendix C – Effectiveness evidence study selection



1 Appendix D – Effectiveness evidence

2 Systematic review

3 Bui, 2020

Bibliographic Reference	Bui, Kim Tam; Willson, Melina L; Goel, Shom; Beith, Jane; Goodwin, Annabel; Ovarian suppression for adjuvant treatment of hormone receptor-positive early breast cancer.; The Cochrane database of systematic reviews; 2020; vol. 3; cd013538

4 Study Characteristics

Study design	Systematic review
Study details	Dates searched 17 September 2018 and top-up search on 26 September 2019 Databases searched Specialised Register of the Cochrane Breast Cancer Group Cochrane Central Register of Controlled Trials MEDLINE (via OvidSP) Embase (via OvidSP) World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal ClinicalTrials.gov register Sources of funding Funded by the National Institute for Health Research (NIHR) Cochrane Incentive Award 2018 (NIHR 128381)
Inclusion criteria	Types of studies Randomised controlled studies Studies published as full text articles or as conference abstracts Types of participants Premenopausal women with a histological diagnosis of hormone receptor-positive early breast cancer. 'Early breast cancer' was defined as tumour-node-metastasis (TNM) stage I, II, and III. 'Premenopausal' was defined by the studies, usually as menses in the last 3 to 12 months and/or oestradiol levels in premenopausal ranges. Types of interventions Intervention: any form of OFS (i.e. oophorectomy, radiation-induced ovarian ablation, or LHRH agonists). LHRH agonists could include buserelin, goserelin, leuprorelin, nafarelin, and triptorelin, and had to be used for at least 12 months. Comparator: any regimen that did not contain OFS. Endocrine therapy and chemotherapy were allowed if the same treatment was given to both groups.
Exclusion criteria	Types of studies Quasi-randomised studies were not eligible Types of participants

	Studies of women with metastatic disease
Intervention(s)	Tamoxifen combined with ovarian function suppression Tamoxifen alone
Outcome(s)	Primary outcomes Overall survival (OS), defined as the time from date randomised to date of death due to any cause Disease-free survival (DFS), defined as the time from date randomised to first recurrence, contralateral breast cancer, second breast cancer, or death, or as defined by the study Secondary outcomes Contralateral breast cancer Second malignancy Adverse events including hot flushes, mood disorders, reduced bone density, arthralgias, altered sexual function, increased cardiovascularrisk, deep vein thrombosis, pulmonary embolism, impaired cognitive function, treatment-related death, and any other significant toxicities reported by the studies. Toxicities could be defined as per the World Health Organization (WHO)/National Cancer Institute of Canada (NCIC) toxicity criteria, or as per the study Compliance with treatment Quality of life, assessed by validated or trial specific instruments such as the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire
Number of studies included in the systematic review	15
Studies from the systematic review that are relevant for use in the current review	ABCTCG 2007 E-3193, INT-0142 (Tevaarwerk et al. 2014) SOFT (Francis et al. 2015) Yang et al. 2013 Yi et al. 2016 ZBCSG Trial B (Mitsuyama et al. 2005)
Studies from the systematic review that are not relevant for use in the current review	OFS versus observation: ZIPP (Baum et al. 2006) OFS + chemotherapy versus chemotherapy: six studies (Arriagada et al. 2005; ECOG 5188, INT-0101 [Davidson et al. 2005]; GABG IV-B-93 [Kaufmann et al. 2007]; IBCSG II [Castiglione-Gertsch et al. 1994]; IBCSG VIII [Karlsson et al. 2011]; SWOG 1996 [Rivkin et al. 1996]). OFS + chemotherapy + tamoxifen versus chemotherapy + tamoxifen: two studies (ASTRRA [Kim et al. 2019]; Uslu et al. 2014).
Additional comments	Data was extracted directly from Baum et al. 2006 for the comparison of OFS + tamoxifen versus tamoxifen alone and only for the subgroup data on ER positive breast cancer Data was extracted directly from ASTRRA (Kim et al. 2020; Baek et al. 2023) for the comparison of OFS + tamoxifen versus tamoxifen alone

	Data was extracted directly from SOFT (Francis et al. 2015) because Bui et al. 2020 reported 8 years follow-up data and we took 5 years follow-up data from Francis et al. 2015 and 12 years follow-up data from Francis et al. 2023 (longest follow-up data published after Bui et al. 2020) The following data was extracted from Bui et al. 2020 for each study: Overall survival: ABCTCG; E-3193, INT-0142; Yang et al. 2013 Disease-free survival: E-3193, INT-0142; Yang et al. 2013 Adverse events: Yi et al. 2016; ZBCSG Trial B Subgroup data for overall survival and disease-free survival: Duration of OFS: E-3193, INT-0142; Yang et al. 2013; ZBCSG Trial B Method of OFS: E-3193, INT-0142; Yang et al. 2013 Lymph node status: ABCTCG; E-3193, INT-0142; Use of chemotherapy: E-3193, INT-0142;

Study arms

Tamoxifen combined with OFS (N = 698)

Tamoxifen alone (N = 744)

Critical appraisal - ROBIS checklist

Section	Question	Answer
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Partially applicable

Randomised controlled trials included in Bui et al. 2020

For RCTs that were included in Bui et al. 2020 see the evidence tables provided in that review for study characteristics and full risk of bias assessments.

Overall risk of bias and applicability for studies included in Bui et al. 2020

Overall risk of bias and applicability for the relevant studies from the Cochrane review was determined by NICE (see section 1.1.3 Methods and process for more details).

Adjuvant Breast Cancer Trials Collaborative (ABCTCG), 2007

Bibliographic Reference	ABCTG; Adjuvant Breast Cancer Trials Collaborative, Group; Ovarian ablation or suppression in premenopausal early breast cancer: results from the international adjuvant breast cancer ovarian ablation or suppression randomized trial.; Journal of the National Cancer Institute; 2007; vol. 99 (no. 7); 516-25

Critical appraisal Cochrane Risk of Bias tool Normal RCT

RoB for objective outcomes: overall survival

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(approximately 40% of participants had ER positive breast cancer)*

Francis, 2015 (SOFT)

Bibliographic Reference	Francis, Prudence A; Regan, Meredith M; Fleming, Gini F; Lang, Istvan; Ciruelos, Eva; Bellet, Meritxell; Bonnefoi, Herve R; Climent, Miguel A; Da Prada, Gian Antonio; Burstein, Harold J; Martino, Silvana; Davidson, Nancy E; Geyer, Charles E Jr; Walley, Barbara A; Coleman, Robert; Kerbrat, Pierre; Buchholz, Stefan; Ingle, James N; Winer, Eric P; Rabaglio-Poretti, Manuela; Maibach, Rudolf; Ruepp, Barbara; Giobbie-Hurder, Anita; Price, Karen N; Colleoni, Marco; Viale, Giuseppe; Coates, Alan S; Goldhirsch, Aron; Gelber, Richard D; Adjuvant ovarian suppression in premenopausal breast cancer.; The New England journal of medicine; 2015; vol. 372 (no. 5); 436-46

RoB for objective outcomes: overall survival, disease-free survival, breast cancer mortality, local and/or locoregional recurrence, new contralateral disease, adverse events - treatment-related mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

RoB for subjective outcomes: quality of life, adherence to or completion of treatment, adverse events - treatment-related morbidity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear if there was allocation concealment. Subjective outcomes self-assessed by participants who were aware of treatment allocation)*
Overall bias and Directness	Overall Directness	Directly applicable

Heo, 2017 (reported as Yi 2016 by Bui et al. 2020)

Bibliographic Reference	Heo, Jung-Yoon; Yi, Hawoo; Fava, Maurizio; Mischoulon, David; Kim, Kiwon; Yoon, Sechang; Jeon, Hong Jin; Lee, Jeong Eon; Agoraphobia and Follicle Stimulating Hormone Levels between Tamoxifen and Goserelin versus Tamoxifen Alone in Premenopausal Hormone Receptor-Positive Breast Cancer: A 12-Month

Prospective Randomized Study.; Psychiatry investigation; 2017; vol. 14 (no. 4); 491-498

1 **RoB for subjective outcomes: Adverse events - treatment-related morbidity**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unclear if there was allocation concealment. Subjective outcomes self-assessed by participants who were aware of treatment allocation)*
Overall bias and Directness	Overall Directness	Directly applicable

2 **Mitsuyama, 2005 (ZBCSG Trial B)**

Bibliographic Reference	Mitsuyama, S; Nomura, Y; Ohno, S; Miyauchi, M; Yamamoto, N; Kimura, T; Saku, M; Miura, S; Yoshikawa, N; Tsujinaka, T; et, al.; Assessment of goserelin treatment in adjuvant therapy for premenopausal patients with breast cancer in Japan-zoladex breast cancer study group trial B; Gan to kagaku ryoho. Cancer & chemotherapy; 2005; vol. 32 (no. 13); 2071-2077

3 **RoB for subjective outcomes: Adverse events - treatment-related morbidity**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unclear if random sequence was generated appropriately, and unclear if allocation sequence was concealed. Unclear risk for detection bias: assessment of patient-reported outcomes could have been influenced by knowledge of the treatment)*
Overall bias and Directness	Overall Directness	Directly applicable

4 **Tevaarwerk, 2014 (E-3193, INT-0142)**

Bibliographic Reference	Tevaarwerk, Amye J; Wang, Molin; Zhao, Fengmin; Fetting, John H; Cella, David; Wagner, Lynne I; Martino, Silvana; Ingle, James N; Sparano, Joseph A; Solin, Lawrence J; Wood, William C; Robert, Nicholas J; Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node negative, hormone receptor-positive breast cancer (E-3193, INT-0142): a trial of the Eastern Cooperative Oncology Group.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2014; vol. 32 (no. 35); 3948-58

5 **RoB for objective outcomes: Overall survival, disease-free survival**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

RoB for subjective outcomes: quality of life, adherence to or completion of treatment, adverse events - treatment-related morbidity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Quality of life outcome assessed by patients who knew which treatment they had received)*
Overall bias and Directness	Overall Directness	Directly applicable

Yang, 2013

Bibliographic Reference	Yang, H; Zong, X; Yu, Y; Shao, G; Zhang, L; Qian, C; Bian, Y; Xu, X; Sun, W; Meng, X; Ding, X; Chen, D; Zou, D; Xie, S; Zheng, Y; Zhang, J; He, X; Sun, C; Yu, X; Ni, J; Combined effects of goserelin and tamoxifen on estradiol level, breast density, and endometrial thickness in premenopausal and perimenopausal women with early-stage hormone receptor-positive breast cancer: a randomised controlled clinical trial.; British journal of cancer; 2013; vol. 109 (no. 3); 582-8

RoB for objective outcomes: overall survival, disease-free survival

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Unclear if allocation sequence was concealed. High risk of attrition bias and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

Randomised controlled trials not included in Bui et al. 2020

Baek, 2023

Bibliographic Reference	Baek, Soo Yeon; Noh, Woo Chul; Ahn, Sei-Hyun; Kim, Hyun-Ah; Ryu, Jai Min; Kim, Seung Il; Lee, Eun-Gyeong; Im, Seock-Ah; Jung, Yongsik; Park, Min Ho; Park, Kyong Hwa; Kang, Su Hwan; Jeong, Joon; Park, Eunhwa; Kim, Sung Yong; Lee, Min Hyuk; Kim, Lee Su; Lim, Woosung; Kim, Seonok; Kim, Hee Jeong; Adding Ovarian Suppression to Tamoxifen for Premenopausal Women With Hormone Receptor-Positive Breast Cancer After Chemotherapy: An 8-Year Follow-Up of the ASTRRA Trial.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2023; vol. 41 (no. 31); 4864-4871

1 **Study details**

Secondary publication of another included study- see primary study for details	ASTRRA, Kim 2020

2 **Baum, 2006 (ZIPP)**

Bibliographic Reference	Baum, M; Hackshaw, A; Houghton, J; Rutqvist; Fornander, T; Nordenskjold, B; Nicolucci, A; Sainsbury, R; Adjuvant goserelin in premenopausal patients with early breast cancer: Results from the ZIPP study.; European journal of cancer (Oxford, England : 1990); 2006; vol. 42 (no. 7); 895-904

3 **Study details**

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	ZIPP (Multicentre), Hackshaw, 2009
Trial registration number and/or trial name	ZIPP Trial registration number not reported
Study location	Italy, Sweden, UK
Study setting	Not reported
Study dates	August 1987 to March 1999
Sources of funding	Drugs supplied by ICI (now Astra Zeneca) for the CRUK BCTG and GIVIO trials. Payment towards the cost of IHC estimation of ERs in UK patients was also given. The UK trial was supported by a grant from the CRUK (formally Cancer Research Campaign). In Italy the coordination of the trial was supported by an educational grant from AstraZeneca. The Stockholm trial received funding from the King Gustaf V Jubilee Fund and an unrestricted research grant from AstraZeneca.

Inclusion criteria	Premenopausal aged women aged 50 years or under with operable stage 1 or 2 breast cancer, regardless of ER status. Invasive breast cancer confined to one breast No evidence of distant metastases following x-ray of the chest, spine and pelvis Normal liver and renal function and full blood counts
Exclusion criteria	Hormonal therapy within the 6 weeks prior to joining the trial Unsuitable for surgery (or radiotherapy, if relevant) Severely limited life expectancy due to intercurrent illness Previous treatment for other malignancies (with the exception of basal or squamous cell carcinoma of the skin, or adequately biopsied in situ carcinoma of the cervix) Primary carcinoma fixed to underlying muscle of chest wall, or was ulcerated, had skin infiltration or presence of axillary nodes that demonstrated deep fixity
Intervention(s)	Tamoxifen combined with ovarian function suppression Tamoxifen 20 mg or 40 mg daily, oral, and ovarian function suppression. Ovarian function suppression using goserelin 3.6 mg subcutaneous injection into the abdominal wall every 28 days. Randomised therapy was continued for 2 years. Local treatment (surgery with or without radiotherapy) and adjuvant chemotherapy (where appropriate) were planned according to local treatment policies prior to randomisation. Peri-operative cyclophosphamide or six cycles of cyclophosphamide/methotrexate/5-fluorouracil chemotherapy was recommended in the protocol but some centres used a standard 5-fluoruocil/epirubicin/cyclophosphamide regimen).
Comparator	Tamoxifen Tamoxifen 20 mg or 40 mg daily, oral. Randomised therapy was continued for 2 years. Local treatment (surgery with or without radiotherapy) and adjuvant chemotherapy (where appropriate) were planned according to local treatment policies prior to randomisation. Peri-operative cyclophosphamide or six cycles of cyclophosphamide/methotrexate/5-fluorouracil chemotherapy was recommended in the protocol but some centres used a standard 5-fluoruocil/epirubicin/cyclophosphamide regimen).
Outcome measures	Overall survival
Number of participants	2710
Percentage of participants with ER positive breast cancer	51.5% overall
Duration of follow-up	5.5 years median follow-up
Methods of analysis	All analyses were performed on an intention to treat basis

Study arms

Tamoxifen combined with ovarian function suppression (N = 1354)

Tamoxifen 20 mg or 40 mg daily, oral, and ovarian function suppression. Ovarian function suppression using goserelin 3.6 mg subcutaneous injection into the abdominal wall every 28 days. Randomised therapy was continued for 2 years. Local treatment (surgery with or without radiotherapy) and adjuvant chemotherapy (where appropriate) were planned according to local treatment policies prior to randomisation. Peri-operative cyclophosphamide or six cycles of cyclophosphamide/methotrexate/5-fluorouracil chemotherapy was recommended in the protocol but some centres used a standard 5-fluoruocil/epirubicin/cyclophosphamide regimen).

Tamoxifen (N = 1356)

Additional comments	Study reports data from 4 trials in the ZIPP collaboration: CRUK BTG Stockholm SE Sweden GIVIO

Tamoxifen 20 mg or 40 mg daily, oral. Randomised therapy was continued for 2 years. Local treatment (surgery with or without radiotherapy) and adjuvant chemotherapy (where appropriate) were planned according to local treatment policies prior to randomisation. Peri-operative cyclophosphamide or six cycles of cyclophosphamide/methotrexate/5-fluorouracil chemotherapy was recommended in the protocol but some centres used a standard 5-fluoruocil/epirubicin/cyclophosphamide regimen).

Characteristics

Arm-level characteristics

Characteristic	Tamoxifen combined with ovarian function suppression (N = 1354)	Tamoxifen (N = 1356)
Female No of events	n = 1354 ; % = 100	n = 1356 ; % = 100
Age Median (IQR)	44 (22 to 56)	44 (21 to 55)
Method of ovarian function suppression No of events		
Goserelin No of events	n = 1354 ; % = 100	n = 1356 ; % = 100
Duration of ovarian function suppression (years) Nominal	2	2
Breast cancer stage Tumour size No of events		

Characteristic	Tamoxifen combined with ovarian function suppression (N = 1354)	Tamoxifen (N = 1356)
≤10 mm **No of events**	n = 148 ; % = 11	n = 159 ; % = 12
11-20 mm No of events	n = 604 ; % = 45	n = 603 ; % = 44
21-50 mm No of events	n = 454 ; % = 33	n = 449 ; % = 33
>50 mm No of events	n = 28 ; % = 2	n = 38 ; % = 3
Unknown No of events	n = 120 ; % = 9	n = 107 ; % = 8
Breast cancer grade No of events	n = NR ; % = NR	n = NR ; % = NR
Lymph node status No of events		
Negative No of events	n = 722 ; % = 53	n = 713 ; % = 53
Positive No of events	n = 558 ; % = 41	n = 571 ; % = 42
Unknown No of events	n = 74 ; % = 5	n = 72 ; % = 5
Chemotherapy use No of events		
Yes No of events	n = 583 ; % = 43	n = 590 ; % = 44
No No of events	n = 766 ; % = 56	n = 761 ; % = 56
Unknown No of events	n = 5 ; % = 1	n = 5 ; % = 1

1 **Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

2 **RoB for objective outcomes: OS, DFS**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Combined analysis of data from 4 sites. There was a shared protocol which could be adapted to suit local requirements. There were some differences in patient population and intervention)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(approximately 50% of participants had ER positive breast cancer)*

1 **Francis, 2023**

Bibliographic Reference	Francis, Prudence A; Fleming, Gini F; Lang, Istvan; Ciruelos, Eva M; Bonnefoi, Herve R; Bellet, Meritxell; Bernardo, Antonio; Climent, Miguel A; Martino, Silvana; Bermejo, Begona; Burstein, Harold J; Davidson, Nancy E; Geyer, Charles E Jr; Walley, Barbara A; Ingle, James N; Coleman, Robert E; Muller, Bettina; Le Du, Fanny; Loibl, Sibylle; Winer, Eric P; Ruepp, Barbara; Loi, Sherene; Colleoni, Marco; Coates, Alan S; Gelber, Richard D; Goldhirsch, Aron; Regan, Meredith M; Adjuvant Endocrine Therapy in Premenopausal Breast Cancer: 12-Year Results From SOFT.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2023; vol. 41 (no. 7); 1370-1375

2 **Study details**

Secondary publication of another included study- see primary study for details	SOFT, Francis 2015

3 **Francis, 2018**

Bibliographic Reference	Francis, Prudence A; Pagani, Olivia; Fleming, Gini F; Walley, Barbara A; Colleoni, Marco; Lang, Istvan; Gomez, Henry L; Tondini, Carlo; Ciruelos, Eva; Burstein, Harold J; Bonnefoi, Herve R; Bellet, Meritxell; Martino, Silvana; Geyer, Charles E Jr; Goetz, Matthew P; Stearns, Vered; Pinotti, Graziella; Puglisi, Fabio; Spazzapan, Simon; Climent, Miguel A; Pavesi, Lorenzo; Ruhstaller, Thomas; Davidson, Nancy E; Coleman, Robert; Debled, Marc; Buchholz, Stefan; Ingle, James N; Winer, Eric P; Maibach, Rudolf; Rabaglio-Poretti, Manuela; Ruepp, Barbara; Di Leo, Angelo; Coates, Alan S; Gelber, Richard D; Goldhirsch, Aron; Regan, Meredith M; Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer.; The New England journal of medicine; 2018; vol. 379 (no. 2); 122-137

4 **Study details**

Secondary publication of another included study- see primary study for details	SOFT and TEXT, Pagani 2014

1 Gnant, 2008 (ABCSG-12)

Bibliographic Reference	Gnant, Michael; Mlineritsch, Brigitte; Luschin-Ebengreuth, Gero; Kainberger, Franz; Kassmann, Helmut; Piswanger-Solkner, Jutta Claudia; Seifert, Michael; Ploner, Ferdinand; Menzel, Christian; Dubsky, Peter; Fitzal, Florian; Bjelic-Radisic, Vesna; Steger, Gunther; Greil, Richard; Marth, Christian; Kubista, Ernst; Samonigg, Hellmut; Wohlmuth, Peter; Mittlbock, Martina; Jakesz, Raimund; Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy.; The Lancet. Oncology; 2008; vol. 9 (no. 9); 840-9

2 Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	ABCSG-12, Gnant 2011 ABCSG-12, Gnant 2015
Trial registration number and/or trial name	ABSCG-12 / NCT00295646
Study type	Randomised controlled trial (RCT)
Study location	Austria
Study setting	Not specified
Study dates	Database locked for analysis on 3 December 2007.
Sources of funding	This trial received funding in the form of drug support and other funding from Astra Zeneca, UK and Novartis, Switzerland.
Inclusion criteria	Premenopausal women ≥ 19 years of age who had received surgery for stage I/II oestrogen receptor (ER) positive or progesterone receptor (PgR) positive (or both) breast cancer Karnofsky Index of 70 or greater Fewer than 10 positive lymph nodes Scheduled to receive goserelin for 3 years
Exclusion criteria	T1a (except yT1a), T4d or yT4 breast cancer History of other tumours or cytotoxic chemotherapy (preoperative chemotherapy was allowed) Preoperative radiotherapy Random assignment more than 8 weeks postoperatively

	Pregnancy or lactation (or both) Oral contraception Serum creatinine concentration of 265 umol/L or more Serum calcium concentration of less than 2 mmol/L or more than 3 mmol/L Bisphosphonate or long-term anti-convulsive therapy within 1 year of study entry Current or previous bone disease Long-term corticosteroid therapy Previous adjuvant chemotherapy Osteomalacia or osteogenesis imperfecta Pre-existing osteoporosis Contraindication to trial medication
Intervention(s)	Tamoxifen and ovarian function suppression: 3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with tamoxifen (20 mg daily orally). Tamoxifen and ovarian function suppression and zoledronic acid: 3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with tamoxifen (20 mg daily orally) plus zoledronic acid (4 mg intravenously every 6 months) A history of preoperative chemotherapy was allowed, otherwise cytotoxic chemotherapy was an exclusion criteria.
Comparator	Anastrozole and ovarian function suppression: 3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with anastrozole (1 mg/day orally). Anastrazole and ovarian function suppression and zoledronic: 3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with anastrozole (1 mg/day orally) plus zoledronic acid (4 mg intravenously every 6 months). A history of preoperative chemotherapy was allowed, otherwise cytotoxic chemotherapy was an exclusion criteria.
Outcome measures	Overall survival Disease-free survival Adverse events - treatment-related mortality Adverse events - treatment-related morbidity Bone-mineral density change T-score category change Local and/or locoregional recurrence New contralateral disease Adherence to or completion of treatment (early cessation of treatment)
Number of participants	401
Percentage of participants with ER positive breast cancer	Tamoxifen + OFS = 95% Tamoxifen + OFS + zoledronic acid = 98% Anastrozole + OFS = 93% Anastrozole + OFS + zoledronic acid = 94%

Duration of follow-up	5 years
Methods of analysis	Intention to treat analysis for Bone-mineral density change and T-score category change

Study arms

Tamoxifen and ovarian function suppression (N = 103)

Loss to follow-up	Lost to follow-up not reported

3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with tamoxifen (20 mg daily orally)

Tamoxifen and ovarian function suppression and zoledronic acid (N = 100)

Loss to follow-up	Lost to follow-up not reported

3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with tamoxifen (20 mg daily orally) plus zoledronic acid (initial dose of 8 mg intravenously, changed to 4 mg, every 6 months, 15 minute infusion time)

Anastrazole and ovarian function suppression (N = 94)

Loss to follow-up	Lost to follow-up not reported

3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with anastrazole (1 mg/day orally)

Anastrazole and ovarian function suppression and zoledronic acid (N = 104)

Loss to follow-up	Lost to follow-up not reported

3 years of goserelin (3.6 mg daily subcutaneously every 28 days) combined with anastrazole (1 mg/day orally) plus zoledronic acid (initial dose of 8 mg intravenously changed to 4 mg intravenously every 6 months, 15 minute infusion time)

Characteristics

Arm-level characteristics

Characteristic	Tamoxifen and ovarian function suppression (N = 103)	Tamoxifen and ovarian function suppression and zoledronic acid (N = 100)	Anastrazole and ovarian function suppression (N = 94)	Anastrazole and ovarian function suppression and zoledronic acid (N = 104)
Female Sample size	n = 103 ; % = 100	n = 100 ; % = 100	n = 94 ; % = 100	n = 104 ; % = 100
Age (years) Median (IQR)	46.6 (31.8 to 54.9)	43.8 (28.1 to 54.7)	45.7 (25.9 to 56.2)	44.7 (30.6 to 55)

Characteristic	Tamoxifen and ovarian function suppression (N = 103)	Tamoxifen and ovarian function suppression and zoledronic acid (N = 100)	Anastrazole and ovarian function suppression (N = 94)	Anastrazole and ovarian function suppression and zoledronic acid (N = 104)
Method of ovarian function suppression Sample size				
Goserelin Sample size	n = 103 ; % = 100	n = 100 ; % = 100	n = 94 ; % = 100	n = 104 ; % = 100
Duration of ovarian function suppression (years) Mean (SD)	3 (NA)	3 (NA)	3 (NA)	3 (NA)
Breast cancer stage Sample size				
T1a Sample size	n = 1 ; % = 1	n = 0 ; % = 0	n = 0 ; % = 0	n = 2 ; % = 2
T1b Sample size	n = 18 ; % = 17	n = 14 ; % = 14	n = 19 ; % = 20	n = 18 ; % = 17
T1c Sample size	n = 56 ; % = 54	n = 55 ; % = 55	n = 50 ; % = 53	n = 58 ; % = 56
T2 Sample size	n = 25 ; % = 24	n = 30 ; % = 30	n = 23 ; % = 24	n = 24 ; % = 23
T3 Sample size	n = 2 ; % = 2	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 1
Breast cancer grade Sample size				
Grade 1 Sample size	n = 17 ; % = 17	n = 20 ; % = 20	n = 11 ; % = 12	n = 14 ; % = 13
Grade 2 Sample size	n = 56 ; % = 54	n = 51 ; % = 51	n = 54 ; % = 57	n = 64 ; % = 62
Grade 3 Sample size	n = 27 ; % = 26	n = 27 ; % = 27	n = 25 ; % = 27	n = 23 ; % = 22
Unknown Sample size	n = 2 ; % = 2	n = 1 ; % = 1	n = 2 ; % = 2	n = 2 ; % = 2

Characteristic	Tamoxifen and ovarian function suppression (N = 103)	Tamoxifen and ovarian function suppression and zoledronic acid (N = 100)	Anastrazole and ovarian function suppression (N = 94)	Anastrazole and ovarian function suppression and zoledronic acid (N = 104)
Lymph node status **Lymph node metastases** Sample size				
Positive Sample size	n = 43 ; % = 42	n = 40 ; % = 40	n = 35 ; % = 37	n = 40 ; % = 38
Negative Sample size	n = 59 ; % = 57	n = 59 ; % = 59	n = 57 ; % = 61	n = 62 ; % = 60
Chemotherapy use Sample size	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR	n = NR ; % = NR

RoB for objective outcomes: overall survival, disease-free survival, breast cancer mortality, local and/or locoregional recurrence, new contralateral disease

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (2x2 factorial design evaluation tamoxifen/anastrozole and zoledronic acid/no zoledronic acid [zoledronic acid not a protocol intervention])

RoB for subjective outcomes: adherence to or completion of treatment, adverse events - treatment-related morbidity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Marked as high risk in domain 2B as no per protocol analysis done and this could have affected the osteoporosis outcome. For domain 3.1 - overall 137/404 participants remaining in bone sub study at 5 years [osteoporosis outcome]: high attrition)
Overall bias and Directness	Overall Directness	Partially applicable (2x2 factorial design evaluation tamoxifen/anastrozole and zoledronic acid/no zoledronic acid [zoledronic acid not a protocol intervention])

1 **Gnant, 2011 (ABCSG-12)**

Bibliographic Reference	Gnant, Michael; Mlineritsch, Brigitte; Stoeger, Herbert; Luschin-Ebengreuth, Gero; Heck, Dietmar; Menzel, Christian; Jakesz, Raimund; Seifert, Michael; Hubalek, Michael; Pristauz, Gunda; Bauernhofer, Thomas; Eidtmann, Holger; Eiermann, Wolfgang; Steger, Guenther; Kwasny, Werner; Dubsky, Peter; Hochreiner, Gerhard; Forsthuber, Ernst-Pius; Fesl, Christian; Greil, Richard; Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial.; The Lancet. Oncology; 2011; vol. 12 (no. 7); 631-41

2 **Study details**

Secondary publication of another included study- see primary study for details	ABCSG-12, Gnant 2008

3 **Gnant, 2015 (ABCSG-12)**

Bibliographic Reference	Gnant, M; Mlineritsch, B; Stoeger, H; Luschin-Ebengreuth, G; Knauer, M; Moik, M; Jakesz, R; Seifert, M; Taucher, S; Bjelic-Radisic, V; Balic, M; Eidtmann, H; Eiermann, W; Steger, G; Kwasny, W; Dubsky, P; Selim, U; Fitzal, F; Hochreiner, G; Wette, V; Sevelda, P; Ploner, F; Bartsch, R; Fesl, C; Greil, R; Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12.; Annals of oncology : official journal of the European Society for Medical Oncology; 2015; vol. 26 (no. 2); 313-20

4 **Study details**

Secondary publication of another included study- see primary study for details	ABCSG-12, Gnant 2008

5 **Hackshaw, 2009 (ZIPP)**

Bibliographic Reference	Hackshaw, Allan; Baum, Michael; Fornander, Tommy; Nordenskjold, Bo; Nicolucci, Antonio; Monson, Kathryn; Forsyth, Sharon; Reczko, Krystyna; Johansson, Ulla; Fohlin, Helena; Valentini, Miriam; Sainsbury, Richard; Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer.; Journal of the National Cancer Institute; 2009; vol. 101 (no. 5); 341-9

1 **Study details**

Secondary publication of another included study- see primary study for details	ZIPP (Multicentre), Baum 2006

2 **Kim, 2020 (ASTRRA)**

Bibliographic Reference	Kim, Hyun-Ah; Lee, Jong Won; Nam, Seok Jin; Park, Byeong-Woo; Im, Seock-Ah; Lee, Eun Sook; Jung, Yong Sik; Yoon, Jung Han; Kang, Sung Soo; Lee, Soo-Jung; Park, Kyong Hwa; Jeong, Joon; Cho, Se-Heon; Kim, Sung Yong; Kim, Lee Su; Moon, Byung-In; Lee, Min Hyuk; Kim, Tae Hyun; Park, Chanheun; Jung, Sung Hoo; Gwak, Geumhee; Kim, Jeryong; Kang, Sun Hee; Jin, Young Woo; Kim, Hee Jeong; Han, Se-Hwan; Han, Wonshik; Hur, Min Hee; Noh, Woo Chul; Adding Ovarian Suppression to Tamoxifen for Premenopausal Breast Cancer: A Randomized Phase III Trial.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2020; vol. 38 (no. 5); 434-443

3 **Study details**

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	ASTRRA, Baek 2023
Trial registration number and/or trial name	ASTRRA / NCT00912548
Study location	South Korea
Study setting	Patients were enrolled from 35 locations in South Korea
Study dates	Patients were enrolled between March 2009 and March 2014.
Sources of funding	
Inclusion criteria	Premenopausal women aged 45 years and below with oestrogen receptor (ER) positive, stage I - III, primary invasive breast cancer treated with definitive surgery after completing adjuvant or neoadjuvant chemotherapy.

	Patients were required to have a WHO performance status of 0,1 or 2 and adequate haematologic, hepatic and renal function. Premenopausal status was defined as regular vaginal bleeding history at the time of diagnosis. Oestrogen receptor positivity was defined as an oestrogen receptor level of >10 mol/mg cytosol protein or > 10% positive tumour cells, based on immunohistochemistry report.
Exclusion criteria	Other primary malignancies within the past 5 years (except adequately treated in situ carcinoma of the cervix, basal cell carcinoma, or squamous cell skin carcinoma). Cyclophosphamide, methotrexate and fluorouracil chemotherapy regimen.
Intervention(s)	Tamoxifen 20 mg daily, oral administration for 5 years, combined with ovarian function suppression induced by goserelin 3.6 mg subcutaneous injection every 28 days for 2 years.
Comparator	Tamoxifen 20 mg daily, oral administration for 5 years.
Outcome measures	Overall survival Disease-free survival Local and/or locoregional recurrence New contralateral disease Adherence to or completion of treatment (early cessation of treatment)
Number of participants	N =1293
Percentage of participants with ER positive breast cancer	100% (ER positive in the inclusion criteria).
Duration of follow-up	63 months median follow-up
Loss to follow-up	
Methods of analysis	Intention to treat analysis

Study arms

Tamoxifen combined with ovarian function suppression (N = 635)

Tamoxifen 20 mg daily, oral administration for 5 years, combined with ovarian function suppression induced by goserelin 3.6 mg subcutaneous injection every 28 days for 2 years.

Tamoxifen (N = 647)

Tamoxifen 20 mg daily, oral administration for 5 years.

1 **Characteristics**

2 **Arm-level characteristics**

Characteristic	Tamoxifen combined with ovarian function suppression (N = 635)	Tamoxifen (N = 647)
Female No of events	n = 635 ; % = 100	n = 647 ; % = 100
Age (years) **Age at enrolment** No of events		
< 35 No of events	n = 89 ; % = 14	n = 83 ; % = 12.8
35 - 39 No of events	n = 173 ; % = 27.2	n = 194 ; % = 30
40 - 45 No of events	n = 373 ; % = 58.7	n = 370 ; % = 57.2
Method of ovarian function suppression No of events		
Goserelin No of events	n = 635 ; % = 100	n = 647 ; % = 100
Duration of ovarian function suppression (years) Mean (SD)	2 (0)	2 (0)
Breast cancer stage (cm) **Tumour size** No of events		
less than 2 No of events	n = 310 ; % = 47.9	n = 307 ; % = 48.3
greater than /equal to 2 No of events	n = 337 ; % = 52.1	n = 328 ; % = 51.7
Breast cancer grade **Tumour grade** No of events		
Grade 1 No of events	n = 117 ; % = 18.4	n = 89 ; % = 13.8
Grade 2 No of events	n = 314 ; % = 49.4	n = 314 ; % = 49.4
Grade 3	n = 148 ; % = 23.3	n = 157 ; % = 24.6

Characteristic	Tamoxifen combined with ovarian function suppression (N = 635)	Tamoxifen (N = 647)
No of events		
Lymph node status No of events		
Negative No of events	n = 288 ; % = 45.4	n = 289 ; % = 44.7
Positive No of events	n = 347 ; % = 54.6	n = 358 ; % = 55.3
Chemotherapy use No of events		
Anthracycline plus cyclophosphamide No of events	n = 192 ; % = 30.2	n = 186 ; % = 28.7
Anthracycline plus cyclophosphamide followed by taxane No of events	n = 322 ; % = 50.7	n = 330 ; % = 51
Anthracycline plus taxane No of events	n = 29 ; % = 4.6	n = 29 ; % = 4.5
Anthracycline plus cyclophosphamide and taxane No of events	n = 4 ; % = 0.6	n = 9 ; % = 1.4
Fluorouracil, anthracycline and cyclophosphamide No of events	n = 74 ; % = 11.7	n = 74 ; % = 11.4
Other taxane based regimen No of events	n = 6 ; % = 0.9	n = 7 ; % = 1.1
Other non-taxane based regimen No of events	n = 4 ; % = 0.6	n = 5 ; % = 0.8
Unknown No of events	n = 4 ; % = 0.6	n = 7 ; % = 1.1

RoB for objective outcomes: overall survival, disease-free survival, local and/or locoregional recurrence, new contralateral disease

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

1 Pagani, 2014 (SOFT and TEXT)

Bibliographic Reference	Pagani, Olivia; Regan, Meredith M; Walley, Barbara A; Fleming, Gini F; Colleoni, Marco; Lang, Istvan; Gomez, Henry L; Tondini, Carlo; Burstein, Harold J; Perez, Edith A; Ciruelos, Eva; Stearns, Vered; Bonnefoi, Herve R; Martino, Silvana; Geyer, Charles E Jr; Pinotti, Graziella; Puglisi, Fabio; Crivellari, Diana; Ruhstaller, Thomas; Winer, Eric P; Rabaglio-Poretti, Manuela; Maibach, Rudolf; Ruepp, Barbara; Giobbie-Hurder, Anita; Price, Karen N; Bernhard, Jurg; Luo, Weixiu; Ribi, Karin; Viale, Giuseppe; Coates, Alan S; Gelber, Richard D; Goldhirsch, Aron; Francis, Prudence A; Adjuvant exemestane with ovarian suppression in premenopausal breast cancer.; The New England journal of medicine; 2014; vol. 371 (no. 2); 107-18

2 Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	SOFT and TEXT, Francis 2018 SOFT and TEXT, Pagani 2022
Trial registration number and/or trial name	SOFT/NCT00066690 TEXT/NCT00066703
Study location	Participating centres in Australia, Belgium, Canada, Egypt, Germany, Hungary, India, Italy, Peru, Slovenia, South Africa, Sweden, Switzerland, UK, USA
Study setting	Breast International Group centres and North American Centres.
Study dates	November 2023 to April 2011
Sources of funding	Supported by Pfizer, Ipsen, the International Breast Cancer Study Group and the National Cancer Institute.
Inclusion criteria	Documented premenopausal status Histologically proven operable breast cancer confined to the breast and ipsilateral axilla, with the exception of internal-mammary-node involvement detected by means of sentinel node biopsy Tumour that expressed oestrogen or progesterone receptors in at least 10% of the cells, as assessed with immunohistochemical testing Patients with synchronous bilateral hormone receptor positive breast cancer were eligible Total mastectomy with subsequent optional radiotherapy, or breast-conserving surgery with subsequent radiotherapy.

	Either axillary dissection or a negative sentinel node biopsy was required Macrometastatsis in a sentinel node required axillary dissection or irradiation
Exclusion criteria	Patients in the TEXT trial were not allowed to receive adjuvant oral endocrine therapy before randomisation
Intervention(s)	Tamoxifen 20 mg daily, oral combined with ovarian function suppression, for 5 years. Ovarian function suppression achieved with triptorelin 3.75 mg depot intramuscular injection every 28 days. Bilateral oophorectomy or ovarian irradiation was allowed after at lest 6 months of triptorelin. Chemotherapy was optional. If administered, chemotherapy was started concomitantly with triptorelin; oral endocrine therapy was started 6 to 8 weeks after the initiation of triptorelin.
Comparator	Exemestane 25 mg daily, oral, combined with ovarian function suppression, for 5 years. Ovarian function suppression achieved with triptorelin 3.75 mg depot intramuscular injection every 28 days. Bilateral oophorectomy or ovarian irradiation was allowed after at lest 6 months of triptorelin. Chemotherapy was optional. Chemotherapy was optional. If administered, chemotherapy was started concomitantly with triptorelin; oral endocrine therapy was started 6 to 8 weeks after the initiation of triptorelin.
Outcome measures	Overall survival Disease-free survival Adverse events - treatment-related morbidity Local and/or locoregional recurrence New contralateral disease Adherence to or completion of treatment (early cessation of treatment)
Number of participants	N=4717 (TEXT and SOFT combined)
Percentage of participants with ER positive breast cancer	97% (TEXT and SOFT combined)
Duration of follow-up	68 months median follow-up (TEXT and SOFT combined)
Methods of analysis	Intention to treat

Study arms

Tamoxifen combined with ovarian function suppression (N = 2358)

Loss to follow-up	77/2358 were lost to follow-up (TEXT and SOFT combined)

Tamoxifen 20 mg daily, oral combined with ovarian function suppression, for 5 years. Ovarian function suppression achieved with triptorelin 3.75 mg depot intramuscular injection every 28 days. Bilateral

oophorectomy or ovarian irradiation was allowed after at lest 6 months of triptorelin. Chemotherapy was optional.

Exemestane combined with ovarian function suppression (N = 2359)

Loss to follow-up	74/2672 were lost to follow-up (TEXT and SOFT combined)

Exemestane 25 mg daily, oral, combined with ovarian function suppression, for 5 years. Ovarian function suppression achieved with triptorelin 3.75 mg depot intramuscular injection every 28 days. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin. Chemotherapy was optional.

Characteristics

Arm-level characteristics

Characteristic	Tamoxifen combined with ovarian function suppression (N = 2358)	Exemestane combined with ovarian function suppression (N = 2359)
Female No of events	n = 2344 ; % = 100	n = 2346 ; % = 100
Age (years) Median (IQR)	43 (39 to 47)	43 (39 to 47)
Method of ovarian function suppression No of events		
Triptorelin **Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.** No of events	n = 2344 ; % = 100	n = 2346 ; % = 100
Breast cancer stage **Tumour size** No of events		
less than 1 cm No of events	n = 307 ; % = 13.1	n = 299 ; % = 12.7
1-2 cm No of events	n = 1151 ; % = 49.1	n = 1165 ; % = 49.7
> 2-5 cm No of events	n = 756 ; % = 32.3	n = 759 ; % = 32.4
> 5 cm No of events	n = 91 ; % = 3.9	n = 88 ; % = 3.8
Unknown No of events	n = 39 ; % = 1.7	n = 35 ; % = 1.5
Breast cancer grade		

Characteristic	Tamoxifen combined with ovarian function suppression (N = 2358)	Exemestane combined with ovarian function suppression (N = 2359)
No of events		
Grade 1 No of events	n = 478 ; % = 20.4	n = 489 ; % = 20.9
Grade 2 No of events	n = 1269 ; % = 54.1	n = 1258 ; % = 53.7
Grade 3 No of events	n = 563 ; % = 24	n = 556 ; % = 23.7
Lymph node status No of events		
N0 No of events	n = 1362 ; % = 58.1	n = 1350 ; % = 57.6
N 1-3 No of events	n = 685 ; % = 29.2	n = 715 ; % = 30.5
N 4+ No of events	n = 299 ; % = 12.7	n = 279 ; % = 11.9
Chemotherapy use No of events		
No chemotherapy TEXT No of events	n = 527 ; % = 22.5	n = 526 ; % = 22.4
No chemotherapy SOFT No of events	n = 473 ; % = 20.2	n = 470 ; % = 20
Chemotherapy TEXT No of events	n = 801 ; % = 34.2	n = 806 ; % = 34.4
Prior chemotherapy SOFT No of events	n = 543 ; % = 23.2	n = 544 ; % = 23.2

RoB for objective outcomes: overall survival, disease-free survival, local and/or locoregional recurrence, new contralateral disease, adverse events - treatment-related mortality

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

RoB for subjective outcomes: adherence to or completion of treatment, adverse events - treatment-related morbidity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Missing data: 12.5% (577/4690) withdrew consent/ lost to follow-up for SOFT and TEXT combined. Statistical analysis plan was amended to combine data from SOFT and TEXT)
Overall bias and Directness	Overall Directness	Directly applicable

Pagani, 2023 (SOFT and TEXT)

Bibliographic Reference	Pagani, Olivia; Walley, Barbara A; Fleming, Gini F; Colleoni, Marco; Lang, Istvan; Gomez, Henry L; Tondini, Carlo; Burstein, Harold J; Goetz, Matthew P; Ciruelos, Eva M; Stearns, Vered; Bonnefoi, Herve R; Martino, Silvana; Geyer, Charles E Jr; Chini, Claudio; Puglisi, Fabio; Spazzapan, Simon; Ruhstaller, Thomas; Winer, Eric P; Ruepp, Barbara; Loi, Sherene; Coates, Alan S; Gelber, Richard D; Goldhirsch, Aron; Regan, Meredith M; Francis, Prudence A; Adjuvant Exemestane With Ovarian Suppression in Premenopausal Breast Cancer: Long-Term Follow-Up of the Combined TEXT and SOFT Trials.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2023; vol. 41 (no. 7); 1376-1382

Study details

Secondary publication of another included study- see primary study for details	SOFT and TEXT, Pagani 2014

Perrone, 2019 (HOBOE)

Bibliographic Reference	Perrone, Francesco; De Laurentiis, Michelino; De Placido, Sabino; Orditura, Michele; Cinieri, Saverio; Riccardi, Ferdinando; Ribecco, Angela Stefania; Putzu, Carlo; Del Mastro, Lucia; Rossi, Emanuela; Tinessa, Vincenza; Mosconi, Anna Maria; Nuzzo, Francesco; Di Rella, Francesca; Gravina, Adriano; Iodice, Giovanni; Landi, Gabriella; Pacilio, Carmen; Forestieri, Valeria; Lauria, Rossella; Fabbri, Agnese; Ibrahim, Toni; De Maio, Ermelinda; Barni, Sandro; Gori, Stefania; Simeon, Vittorio; Arenare, Laura; Daniele, Gennaro; Piccirillo, Maria Carmela; Normanno, Nicola; de Matteis, Andrea; Gallo, Ciro; Adjuvant zoledronic acid and letrozole plus ovarian function suppression in premenopausal breast cancer: HOBOE phase 3 randomised trial.; European journal of cancer (Oxford, England : 1990); 2019; vol. 118; 178-186

Study details

Secondary publication of	N/A

another included study- see primary study for details	
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	HOBOE/NCT00412022
Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Study conducted in 16 public Italian institutions
Sources of funding	Trial partially supported by the Associazione Italiana per la Ricereca sul Cancro (grant number 1162). Letrozole (and zoledronic acid) were supplied by Novartis (grant code CZOL446GIT07).
Inclusion criteria	Premenopausal women aged ≥18 years with histologically confirmed breast cancer expressing oestrogen and/or progesterone receptor in at least 1% of tumour cells at immunohistochemistry completely removed by surgery Any pathologic tumour size and axillary nodal status No evidence of recurrence Patients who had received neoadjuvant or adjuvant chemotherapy and/or locoregional radiotherapy could be included Premenopausal status defined as last menstrual cycle within 12 months prior to randomisation. Levels of follicle stimulating hormone (FSH), LH (luteinising-hormone) and oestradiol were not used to define premenopausal status.
Exclusion criteria	Previous malignant neoplasia (excluding adequately treated basal or spinocellular cutaneous carcinoma and in situ carcinoma of the uterine cervix) Previous treatment with tamoxifen or aromatase inhibitors Pregnancy/lactation Serum creatinine level >1.25 times the maximum normal value Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 times the normal value Clinical/radiological evidence of active bone fractures Presence of concomitant disease contraindicating study drugs Current or planned invasive dental therapy
Intervention(s)	Tamoxifen 20 mg/ day orally for 5 years combined with ovarian function suppression (intramuscular triptorelin 3.75 mg at the start of treatment and then every 4 weeks) for 5 years or up to 55 years of age.

	Radiotherapy on the residual breast, lymph node stations and thoracic wall was allowed if indicated by international standards, before or during the hormonal treatment. previous neoadjuvant and/or adjuvant chemotherapy was allowed. Trastuzumab was allowed in patients with HER2 positive breast cancer. Randomisation was performed after completion of surgery and adjuvant chemotherapy. Radiotherapy and trastuzumab could overlap with hormonal treatment.
Comparator	Letrozole 2.5 mg/day for 5 years combined with ovarian function suppression (intramuscular triptorelin 3.75 mg at the start of treatment and then every 4 weeks) for 5 years or up to 55 years of age. Radiotherapy on the residual breast, lymph node stations and thoracic wall was allowed if indicated by international standards, before or during the hormonal treatment. previous neoadjuvant and/or adjuvant chemotherapy was allowed. Trastuzumab was allowed in patients with HER2 positive breast cancer. Randomisation was performed after completion of surgery and adjuvant chemotherapy. Radiotherapy and trastuzumab could overlap with hormonal treatment.
Outcome measures	Overall survival Disease-free survival Adverse events - treatment-related morbidity Local and/or locoregional recurrence New contralateral disease Adherence to or completion of treatment (early cessation of treatment)
Number of participants	N=710 (Tamoxifen and Letrozole arms)
Percentage of participants with ER positive breast cancer	Not reported
Duration of follow-up	64 months median follow-up (48-88 months)
Methods of analysis	Efficacy outcomes analysed using intention to treat approach. Safety outcomes were analysed using per protocol approach.

1 **Study arms**

2 **Tamoxifen combined with ovarian function suppression (N = 354)**

Loss to follow-up	5 participants lost to follow-up (1.4%)

3 **Letrozole combined with ovarian function suppression (N = 356)**

Loss to follow-up	5 participants lost to follow-up (1.4%)

1 **Characteristics**

2 **Arm-level characteristics**

Characteristic	Tamoxifen combined with ovarian function suppression (N = 354)	Letrozole combined with ovarian function suppression (N = 356)
Female No of events	n = 354 ; % = 100	n = 356 ; % = 100
Age (years) Median (IQR)	44.7 (41.3 to 48)	44.9 (40.8 to 48)
Method of ovarian function suppression No of events		
Triptorelin No of events	n = 354 ; % = 100	n = 356 ; % = 100
Duration of ovarian function suppression (years) **5 years** No of events	n = 354 ; % = 100	n = 356 ; % = 100
Breast cancer stage **Pathological tumour category** No of events		
pT1 No of events	n = 243 ; % = 68.6	n = 239 ; % = 67.1
pT2 No of events	n = 92 ; % = 26	n = 99 ; % = 27.8
pT3 No of events	n = 8 ; % = 2.3	n = 10 ; % = 2.8
pT4 No of events	n = 4 ; % = 1.1	n = 3 ; % = 0.8
pTx or unknown No of events	n = 7 ; % = 2	n = 5 ; % = 1.4
Breast cancer grade No of events		
G1 No of events	n = 36 ; % = 10.2	n = 33 ; % = 9.3
G2 No of events	n = 195 ; % = 55.1	n = 177 ; % = 49.7
G3	n = 112 ; % = 31.6	n = 128 ; % = 36

Characteristic	Tamoxifen combined with ovarian function suppression (N = 354)	Letrozole combined with ovarian function suppression (N = 356)
No of events		
Lymph node status **Pathological nodal status** No of events		
pN0 No of events	n = 193 ; % = 54.5	n = 196 ; % = 55.1
pN1 No of events	n = 111 ; % = 31.4	n = 109 ; % = 30.6
pN2 No of events	n = 34 ; % = 9.6	n = 38 ; % = 10.7
pN3 No of events	n = 16 ; % = 4.5	n = 13 ; % = 3.7
Chemotherapy use **Previous chemotherapy use** No of events		
No No of events	n = 132 ; % = 37.3	n = 133 ; % = 37.4
Yes No of events	n = 222 ; % = 62.7	n = 223 ; % = 62.6

RoB for objective outcomes: overall survival, disease-free survival, local and/or locoregional recurrence, new contralateral disease

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

RoB for subjective outcomes: adherence to or completion of treatment, adverse events - treatment-related morbidity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Safety outcomes analysed using per protocol)
Overall bias and Directness	Overall Directness	Directly applicable

1 **Ribi, 2016 (SOFT)**

Bibliographic Reference	Ribi, Karin; Luo, Weixiu; Bernhard, Jurg; Francis, Prudence A; Burstein, Harold J; Ciruelos, Eva; Bellet, Meritxell; Pavesi, Lorenzo; Lluch, Ana; Visini, Marilena; Parmar, Vani; Tondini, Carlo; Kerbrat, Pierre; Perello, Antonia; Neven, Patrick; Torres, Roberto; Lombardi, Davide; Puglisi, Fabio; Karlsson, Per; Ruhstaller, Thomas; Colleoni, Marco; Coates, Alan S; Goldhirsch, Aron; Price, Karen N; Gelber, Richard D; Regan, Meredith M; Fleming, Gini F; Adjuvant Tamoxifen Plus Ovarian Function Suppression Versus Tamoxifen Alone in Premenopausal Women With Early Breast Cancer: Patient-Reported Outcomes in the Suppression of Ovarian Function Trial.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2016; vol. 34 (no. 14); 1601-10

2 **Study details**

Secondary publication of another included study-see primary study for details	SOFT, Francis 2015

3 **Sun, 2021**

Bibliographic Reference	Sun, Dan; Li, Yingchun; Zhang, Xiaoyu; Role of leuprorelin on ovarian function of patients with receptor positive premenopausal breast cancer.; Pakistan journal of pharmaceutical sciences; 2021; vol. 34 (no. 6supplementary); 2379-2383

4 **Study details**

Secondary publication of another included study-see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	Trial registration not reported
Study type	Randomised controlled trial (RCT)
Study location	Cangzhou Central Hospital, China

Study setting	Hospital
Study dates	January 2018 to October 2020
Sources of funding	Not reported
Inclusion criteria	Patients with pathologically confirmed breast cancer who were not menopausal before commencing treatment Immunohistochemical results indicating oestrogen receptor positive and /or progesterone receptor positive breast cancer Patients who had received standard surgery, chemoradiotherapy and other treatments
Exclusion criteria	Patients who did not complete routine adjuvant therapy Patients who had not reached follow-up time terminated treatment by themselves Patients with a second primary cancer Incomplete clinical data Presence of serious neurological diseases or mental health condition Severe heart, kidney, lung or other organ failure disease Coagulation dysfunction
Intervention(s)	Tamoxifen 10 mg twice daily combined with ovarian function suppression with leuporelin 3.75 mg subcutaneous injection once every 4 weeks for 1 year
Comparator	Tamoxifen 10 mg twice daily
Outcome measures	Overall survival
Number of participants	40
Percentage of participants with ER positive breast cancer	All participants had hormone receptor positive breast cancer (oestrogen receptor positive and/or progesterone receptor positive in the inclusion criteria). % with ER positive not reported.
Duration of follow-up	30 months follow-up
Loss to follow-up	Not reported
Methods of analysis	Not stated

Study arms

Tamoxifen combined with ovarian function suppression (N = 20)

Tamoxifen 10 mg twice daily combined with ovarian function suppression with leuporelin 3.75 mg subcutaneous injection once every 4 weeks for 1 year

Tamoxifen (N = 20)

10 mg twice daily

Characteristics

Arm-level characteristics

Characteristic	Tamoxifen combined with ovarian function suppression (N = 20)	Tamoxifen (N = 20)
Female No of events	n = 20 ; % = 100	n = 20 ; % = 100
Age (years) Mean (SD)	41.45 (5.89)	41.25 (5.75)
Method of ovarian function suppression No of events		
Leuporelin No of events	n = 20 ; % = 100	n = 20 ; % = 100
Duration of ovarian function suppression (years) Nominal	1	NA
Breast cancer stage No of events	n = NR ; % = NR	n = NR ; % = NR
Breast cancer grade No of events	n = NR ; % = NR	n = NR ; % = NR
Lymph node status No of events	n = NR ; % = NR	n = NR ; % = NR
Chemotherapy use No of events	n = NR ; % = NR	n = NR ; % = NR

RoB for objective outcomes: overall survival

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (Method of randomisation unclear: "randomised comprehensive sequential method was used". Very limited reporting of baseline characteristics. No information about type of analysis, adherence or missing data)
Overall bias and Directness	Overall Directness	Directly applicable

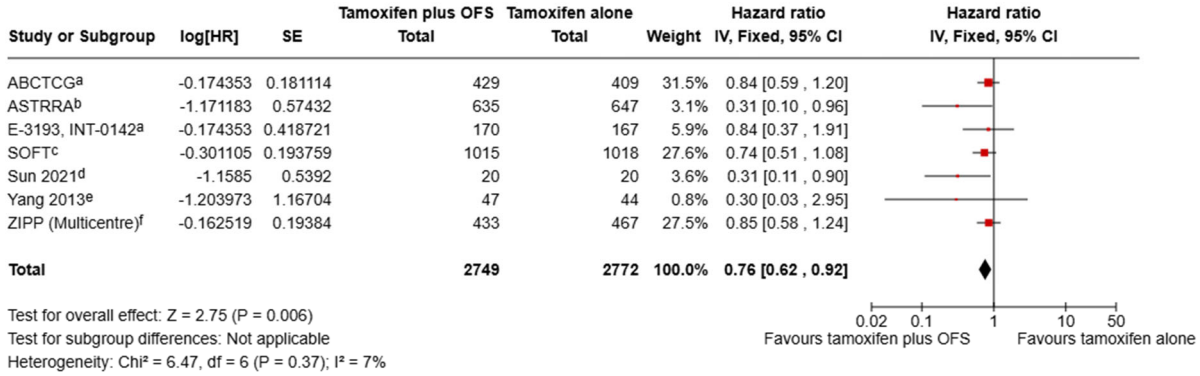
1

Appendix E – Forest plots

Ovarian function suppression combined with tamoxifen compared to tamoxifen alone

Overall survival

Figure 1 Overall survival – 2.5 to 6 years follow-up

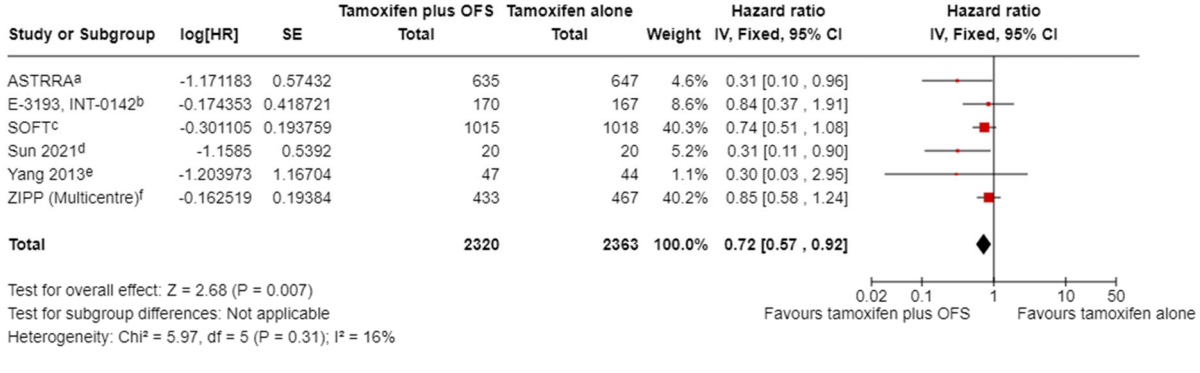


Test for overall effect: Z = 2.75 (P = 0.006)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 6.47, df = 6 (P = 0.37); I² = 7%

Footnotes

[a]Follow-up: 5 years; data reported by Bui et al. (2020)
[b]Follow-up: 5 years; data reported by Kim et al. (2020)
[c]Follow-up: 5 years; data reported by Francis et al. (2015)
[d]Follow-up: 2.5 years; data reported by Sun et al. (2021); log HR and standard error of HR were calculated using number of events and total sample
[e]Follow-up: 6 years; data reported by Bui et al. (2020)
[f]Follow-up: 5 years; Baum et al. (2006) only reported number or events; data taken from the 2018 update of the NICE guideline NG101

Figure 2 Overall survival – 2.5 to 6 years follow-up sensitivity analysis without study with concurrent chemotherapy (ABCTCG study)

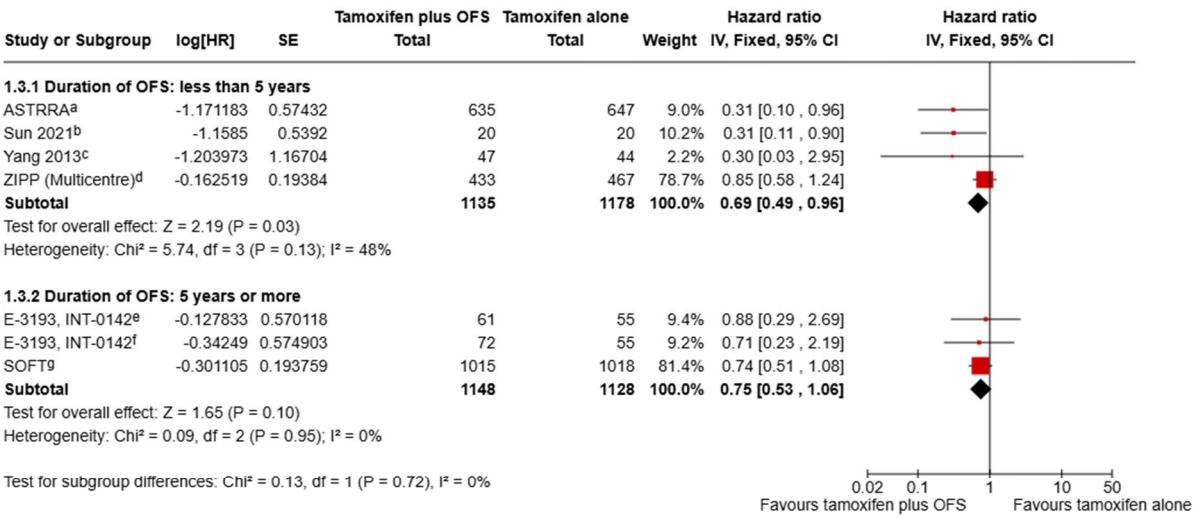


Test for overall effect: Z = 2.68 (P = 0.007)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 5.97, df = 5 (P = 0.31); I² = 16%

Footnotes

[a]Follow-up: 5 years; data reported by Kim et al. (2020)
[b]Follow-up: 5 years; data reported by Bui et al. (2020)
[c]Follow-up: 5 years; data reported by Francis et al. (2015)
[d]Follow-up: 2.5 years; data reported by Sun et al. (2021)
[e]Follow-up: 6 years; data reported by Bui et al. (2020)
[f]Follow-up: 5 years; Baum et al. (2006) only reported number or events; data taken from the 2018 update of the NICE guideline NG101

Figure 3 Overall survival – 2.5 to 6 years follow-up – subgroup analysis by duration of OFS



Footnotes

[a]Follow-up: 5 years; data reported by Kim et al. (2020); goserelin for 2 years

[b]Follow-up: 2.5 years; data reported by Sun et al. (2021); leuprorelin for 1 year

[c]Follow-up: 6 years; data reported by Bui et al. (2020); goserelin for 1.5 years

[d]Follow-up: 5 years; Baum et al. (2006) only reported number or events; data taken from the 2018 update of the NICE guideline NG101; goserelin for 2 years

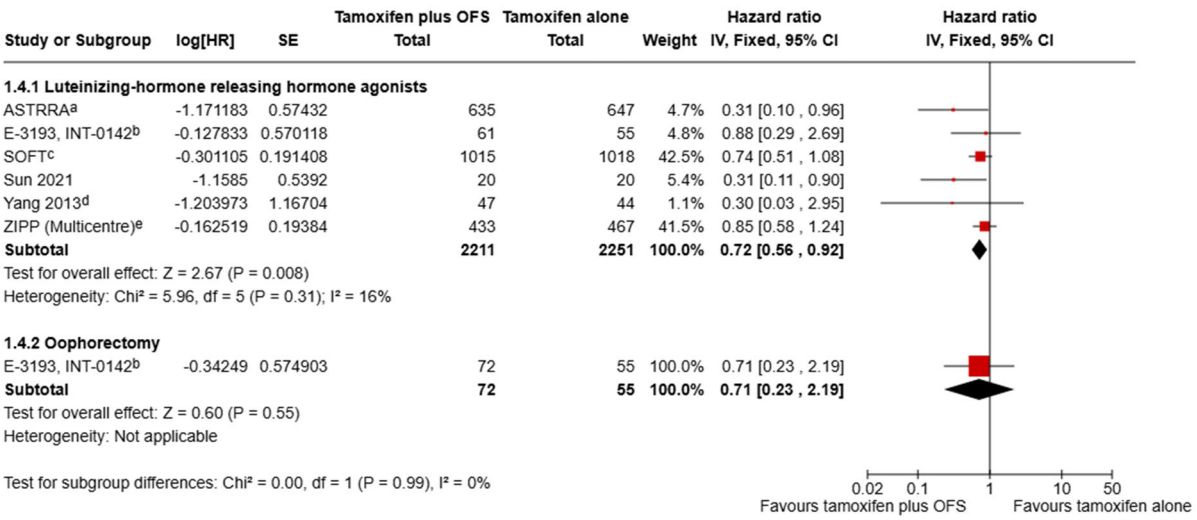
[e]Follow-up: 5 years; data reported by Bui et al. (2020); goserelin or leuprorelin for 5 years

[f]Follow-up: 5 years; data reported by Bui et al. (2020); data is for oophorectomy

[g]Follow-up: 5 years; data reported by Francis et al. (2015); triptorelin for 5 years

Note: The ABCTCG study was not included in this subgroup analysis because 8.4% of participants received goserelin or leuprorelin for at least 2 years, 22.8% had an oophorectomy, and 68.8% had OFS by radiation.

Figure 4 Overall survival – 2.5 to 6 years follow-up – subgroup analysis by method of OFS

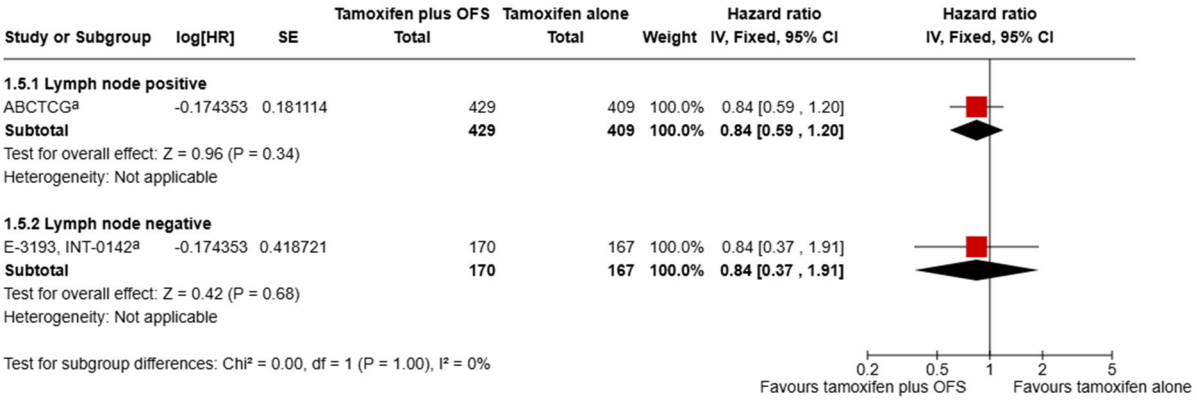


Footnotes

[a]Follow-up: 5 years; data reported by Kim et al. (2020)
[b]Follow-up: 5 years; data reported by Bui et al. (2020)
[c]Follow-up: 5 years; data reported by Francis et al. (2015)
[d]Follow-up: 6 years; data reported by Bui et al. (2020)
[e]Follow-up: 5 years; Baum et al. (2006) only reported number or events; data taken from the 2018 update of the NICE guideline NG101

Note: The ABCTCG study was not included in this subgroup analysis because 8.4% of participants received goserelin or leuprorelin for at least 2 years, 22.8% had an oophorectomy, and 68.8% had OFS by radiation.

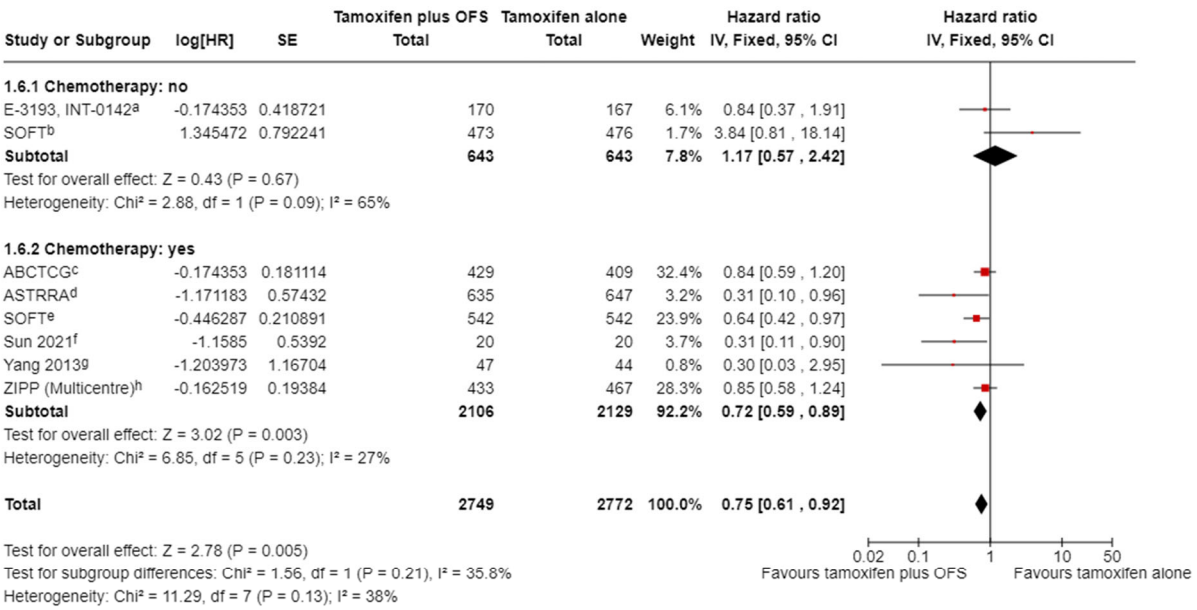
Figure 5 Overall survival – 5 years follow-up – subgroup analysis by lymph node status



Footnotes

[a]Follow-up: 5 years; data reported by Bui et al. (2020)

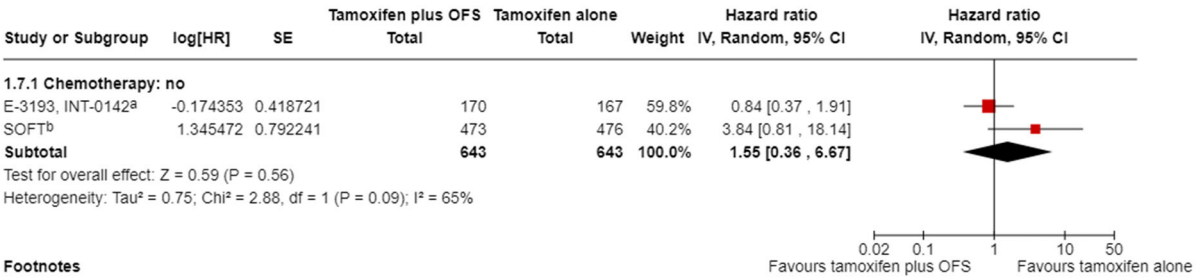
Figure 6 Overall survival – 2.5 to 6 years follow-up – subgroup analysis by use of chemotherapy – FE model



Footnotes

[a]Data reported by Bui et al. (2020); chemotherapy was not permitted prior or during endocrine therapy
[b]Data reported by Francis et al. (2015); all participants without prior chemotherapy
[c]Data reported by Bui et al. (2020); chemotherapy was allowed concurrently with tamoxifen
[d]Data reported by Kim et al. (2020); all participants with prior neoadjuvant or adjuvant chemotherapy
[e]Data reported by Francis et al. (2015); all participants with prior chemotherapy
[f]Data reported by Sun et al. (2021); prior chemotherapy was allowed
[g]Data reported by Bui et al. (2020); prior chemotherapy was allowed
[h]Data taken from the 2018 update of the NICE guideline NG101; prior chemotherapy was allowed

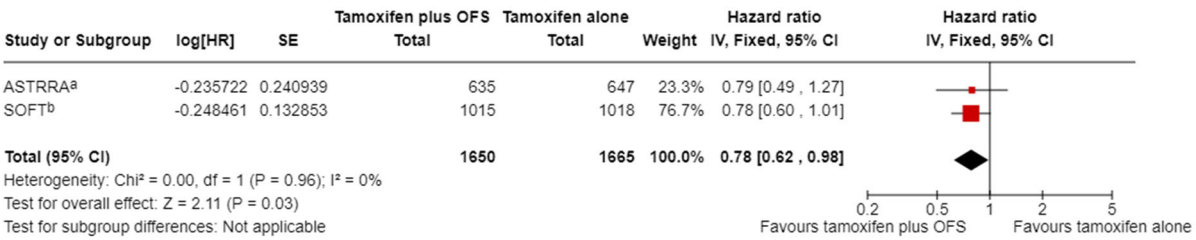
Figure 7 Overall survival – 5 years follow-up – subgroup analysis by use of chemotherapy – RE model (I2 >50%)



Footnotes

[a]Data reported by Bui et al. (2020); chemotherapy was not permitted prior or during endocrine therapy
[b]Data reported by Francis et al. (2015); all participants without prior chemotherapy

Figure 8 Overall survival – 8 to 12 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)

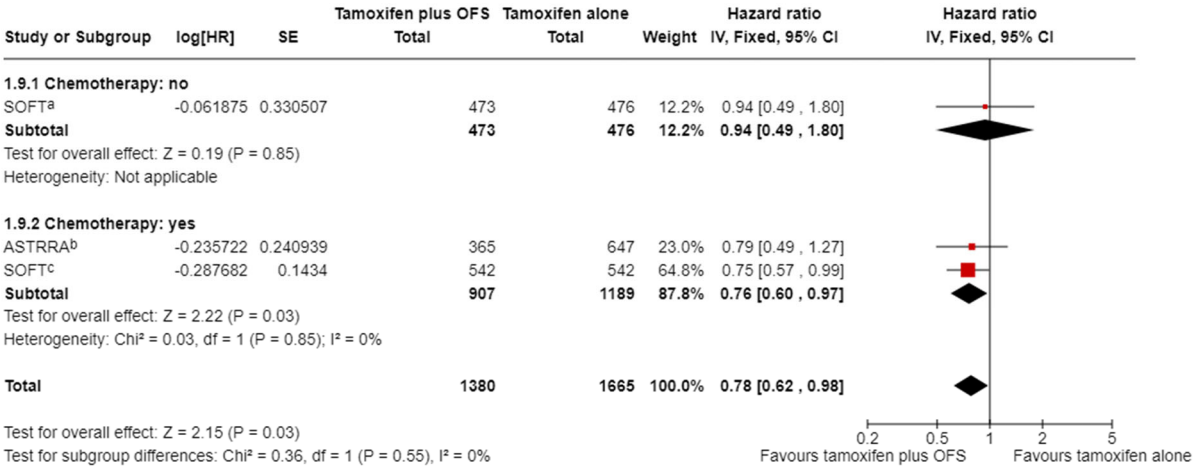


Footnotes

[a]Follow-up: 8 years; data reported by Baek et al. (2023)

[b]Follow-up: 12 years; data reported by Francis et al. (2023)

Figure 9 Overall survival – 8 to 12 years follow-up – subgroup analysis by use of chemotherapy



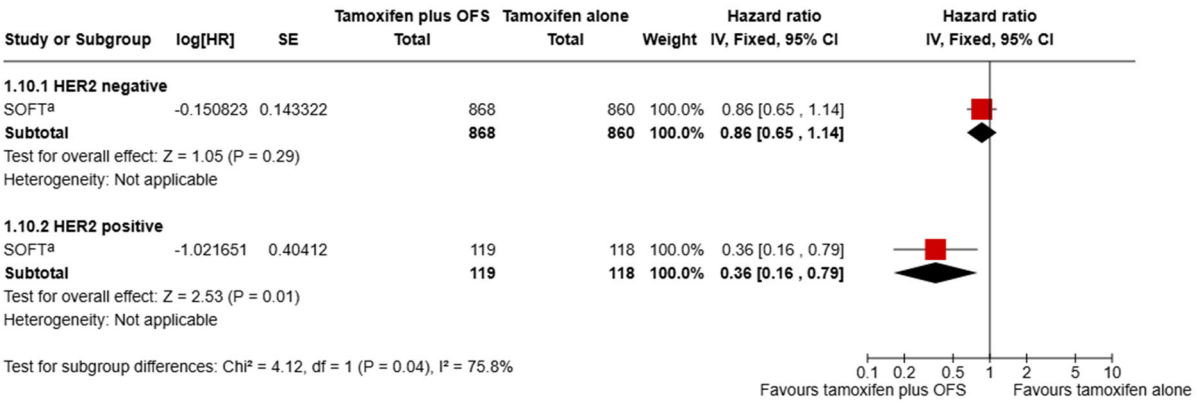
Footnotes

[a]Data reported by Francis et al. (2023); all participants without prior chemotherapy

[b]Data reported by Baek et al. (2023); all participants with prior chemotherapy

[c]Data reported by Francis et al. (2023); all participants with prior chemotherapy

Figure 10 Overall survival – 12 years follow-up – subgroup analysis by HER2 status

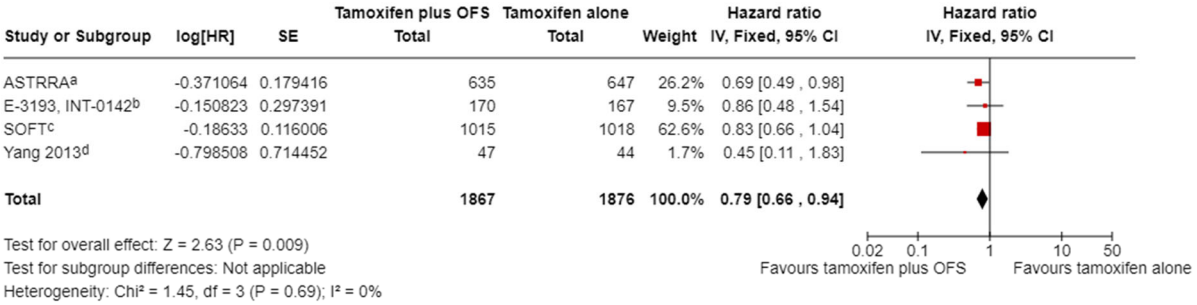


Footnotes

[a]Data reported by Francis et al. (2023)

Disease-free survival

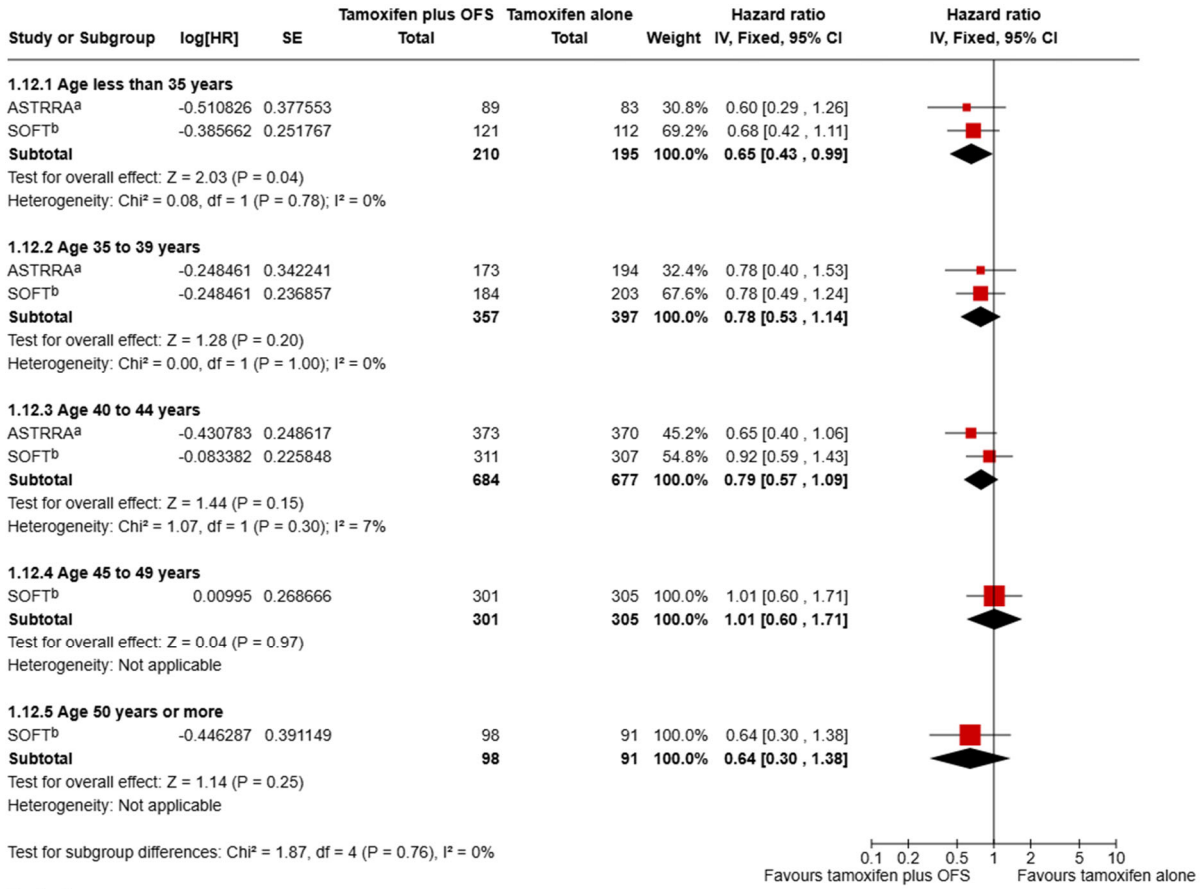
Figure 11 Disease-free survival – 5 to 6 years follow-up



Footnotes

[a]Follow-up: 5 years; data reported by Kim et al. (2020)
[b]Follow-up: 5 years; data reported by Bui et al. (2020)
[c]Follow-up: 5 years; data reported by Francis et al. (2015)
[d]Follow-up: 6 years; data reported by Bui et al. (2020)

Figure 12 Disease-free survival – 5 years follow-up – subgroup analysis by age

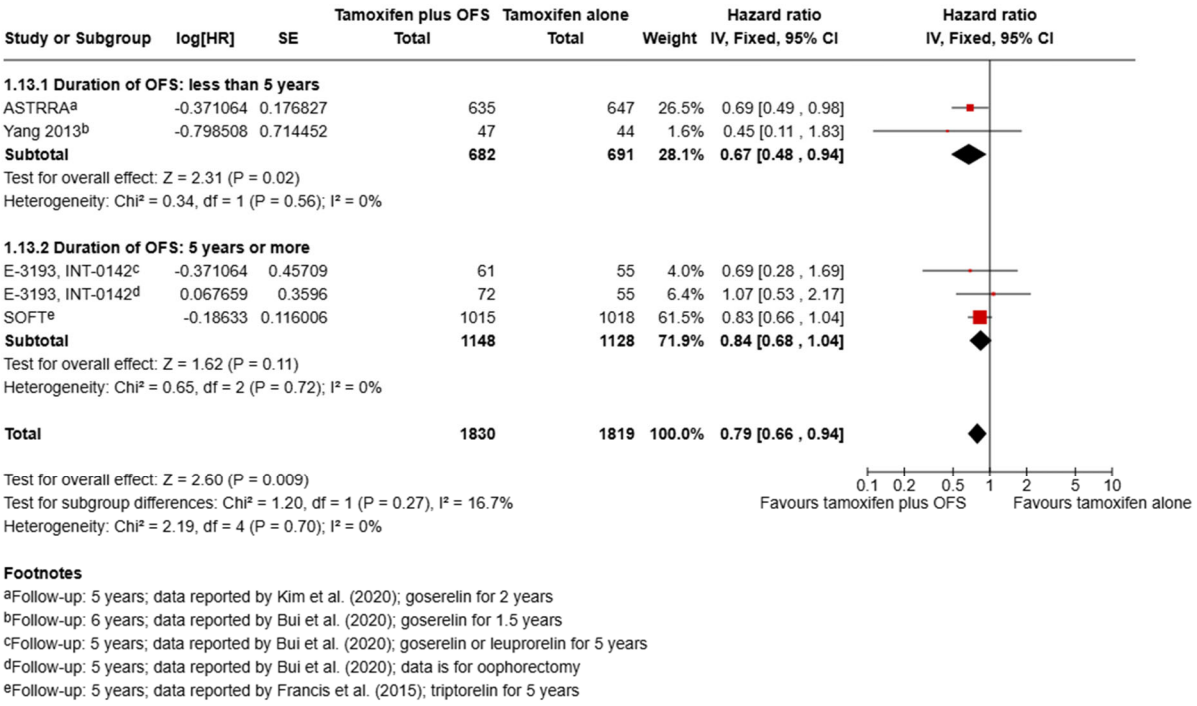


Footnotes

[a]Data reported by Kim et al. (2020)

[b]Data reported by Francis et al. (2015)

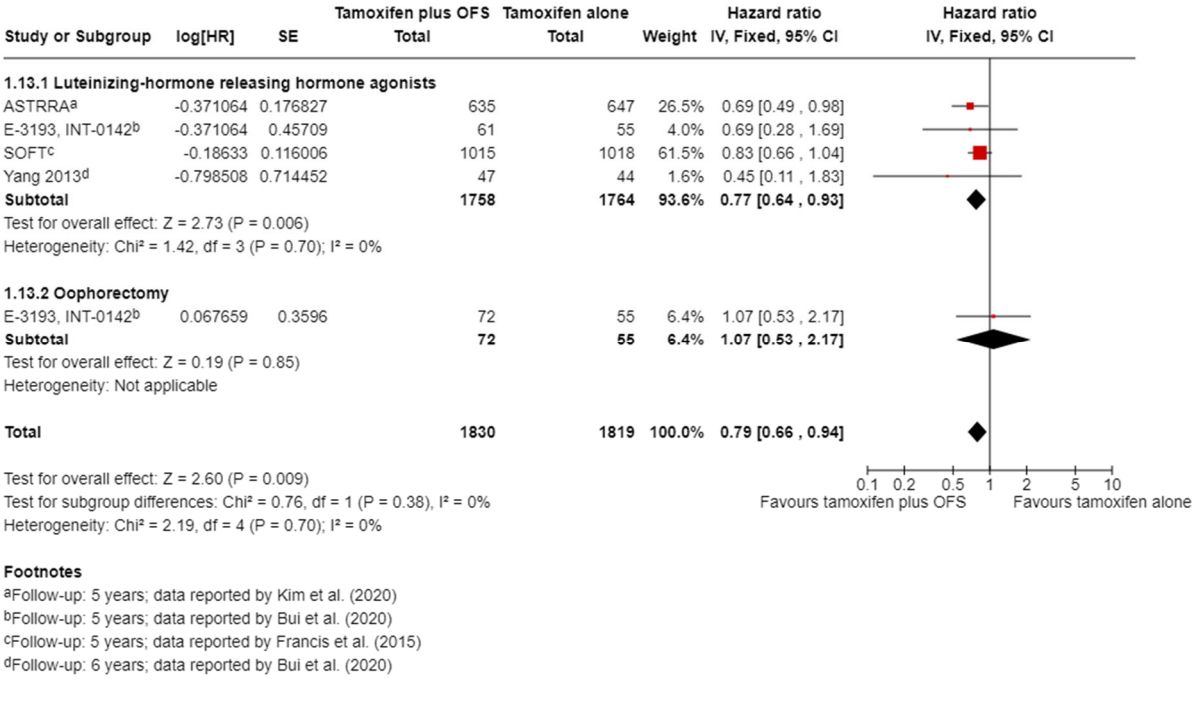
Figure 13 Disease-free survival – 5 to 6 years follow-up – subgroup analysis by duration of OFS



Footnotes

[a]Follow-up: 5 years; data reported by Kim et al. (2020); goserelin for 2 years
[b]Follow-up: 6 years; data reported by Bui et al. (2020); goserelin for 1.5 years
[c]Follow-up: 5 years; data reported by Bui et al. (2020); goserelin or leuprorelin for 5 years
[d]Follow-up: 5 years; data reported by Bui et al. (2020); data is for oophorectomy
[e]Follow-up: 5 years; data reported by Francis et al. (2015); triptorelin for 5 years

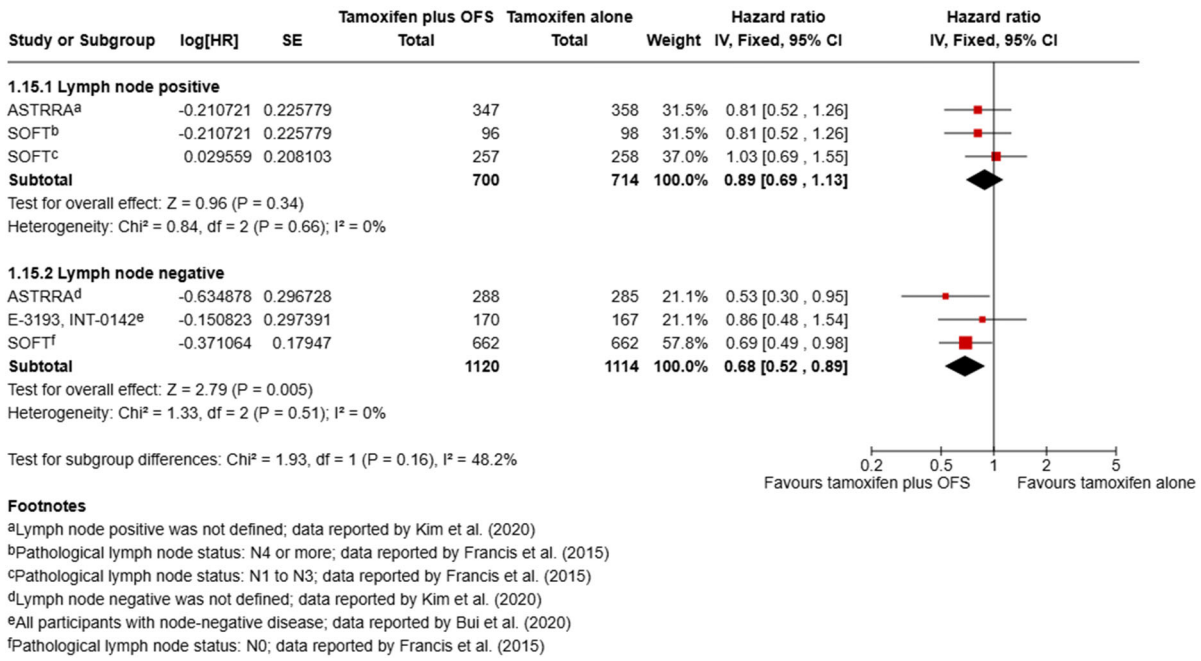
Figure 14 Disease-free survival – 5 to 6 years follow-up - subgroup analysis by method of OFS



Footnotes

[a]Follow-up: 5 years; data reported by Kim et al. (2020)
[b]Follow-up: 5 years; data reported by Bui et al. (2020)
[c]Follow-up: 5 years; data reported by Francis et al. (2015)
[d]Follow-up: 6 years; data reported by Bui et al. (2020)

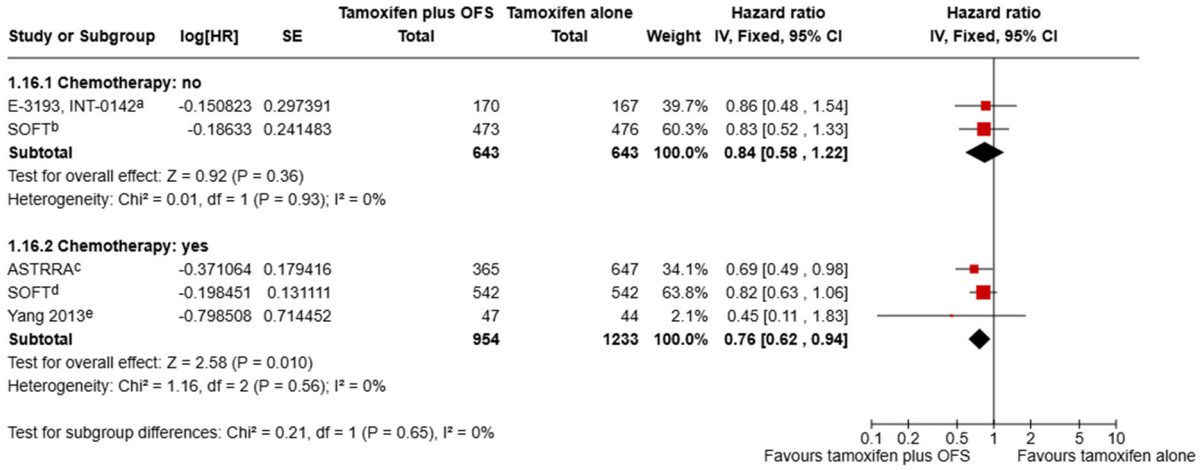
Figure 15 Disease-free survival – 5 years – subgroup analysis by lymph node status



Footnotes

[a]Lymph node positive was not defined; data reported by Kim et al. (2020)
[b]Pathological lymph node status: N4 or more; data reported by Francis et al. (2015)
[c]Pathological lymph node status: N1 to N3; data reported by Francis et al. (2015)
[d]Lymph node negative was not defined; data reported by Kim et al. (2020)
[e]All participants with node-negative disease; data reported by Bui et al. (2020)
[f]Pathological lymph node status: N0; data reported by Francis et al. (2015)

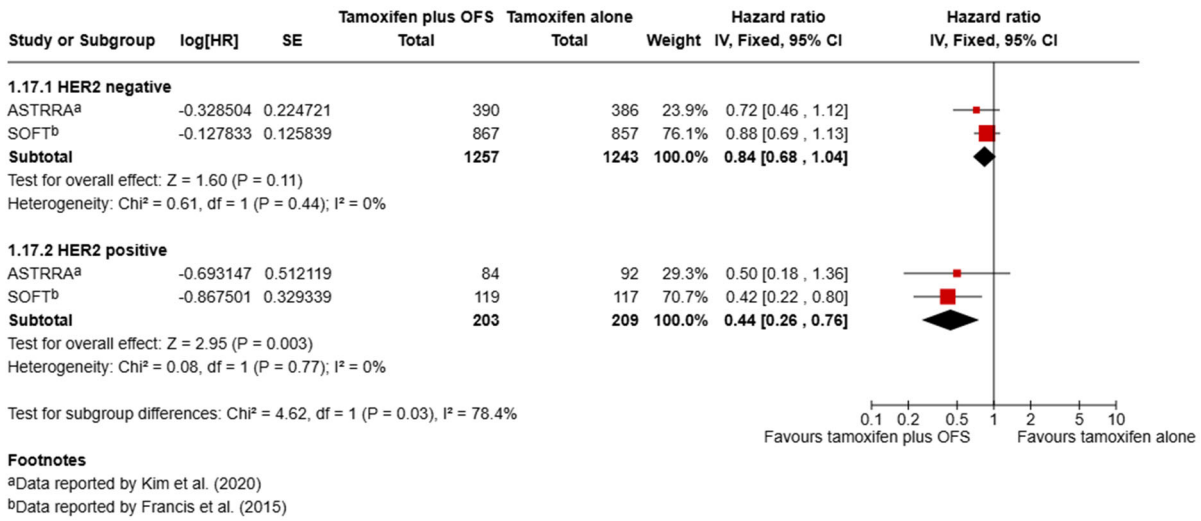
Figure 16 Disease-free survival – 5 to 6 years follow-up – subgroup analysis by use of chemotherapy



Footnotes

[a]Data reported by Bui et al. (2020); chemotherapy was not permitted prior or during endocrine therapy
[b]Data reported by Francis et al. (2015); all participants without prior chemotherapy
[c]Data reported by Kim et al. (2020); all participants with prior chemotherapy
[d]Data reported by Francis et al. (2015); all participants with prior chemotherapy
[e]Data reported by Bui et al. (2020); prior chemotherapy was allowed

Figure 17 Disease-free survival – 5 years follow-up – subgroup analysis by HER2 status

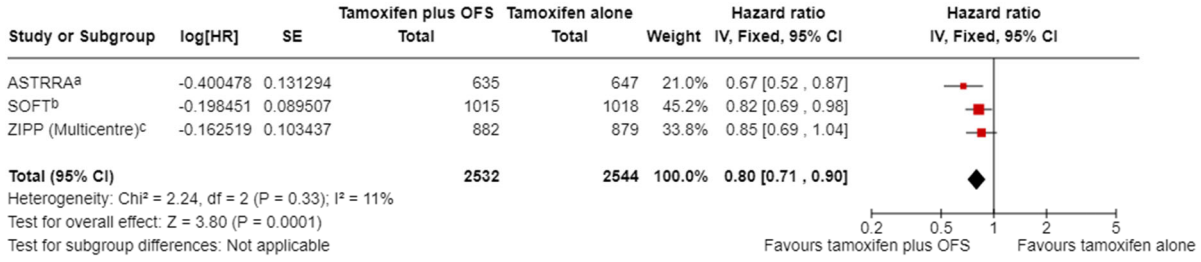


Footnotes

[a]Data reported by Kim et al. (2020)

[b]Data reported by Francis et al. (2015)

Figure 18 Disease-free survival – 8 to 12 years follow-up (all luteinising - hormone releasing hormone agonists)



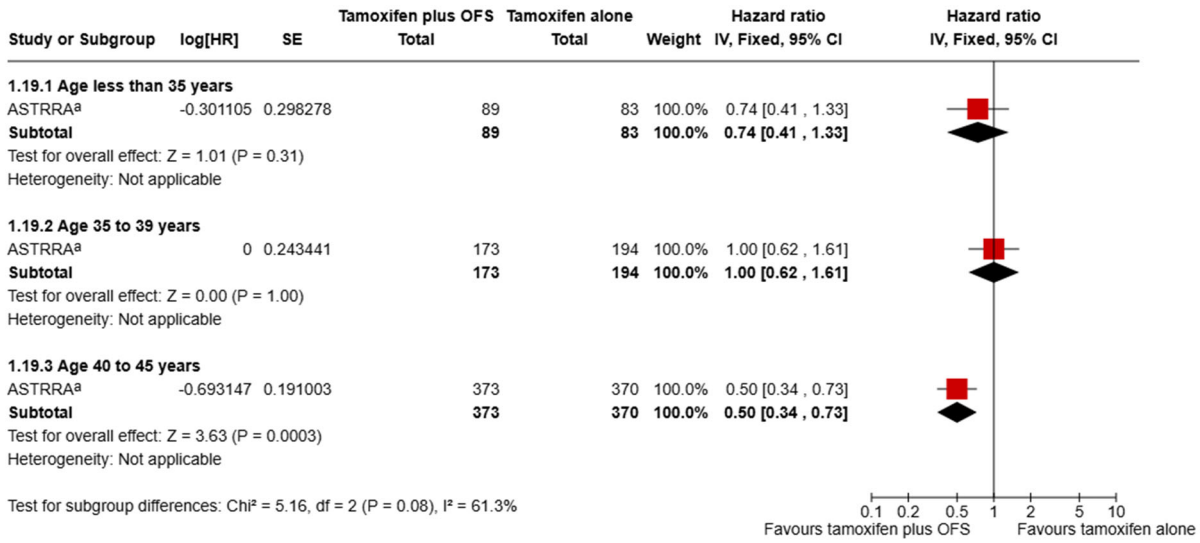
Footnotes

[a]Follow-up: 8 years; data reported by Baek et al. (2023)

[b]Follow-up: 12 years; data reported by Francis et al. (2023)

[c]Follow-up: 12 years; data reported by Hackshaw et al. (2009)

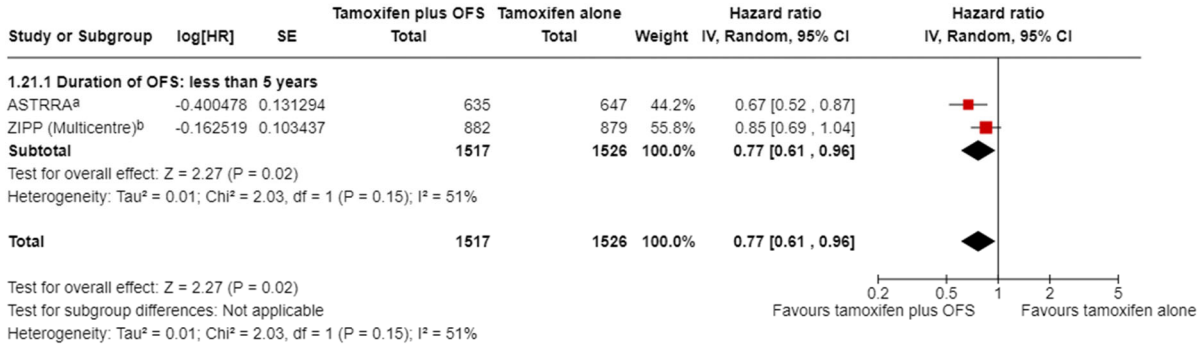
Figure 19 Disease-free survival – 8 to 12 years follow-up- subgroup analysis by age



Footnotes

[a]Data reported by Baek et al. (2023)

Figure 20 Disease-free survival 8 to 12 years follow-up – subgroup analysis by duration of OFS – RE model (I2 >50%)

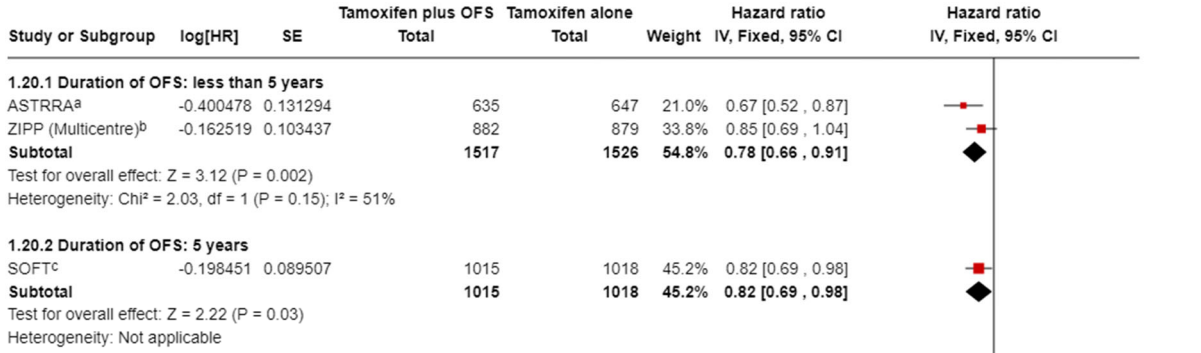


Footnotes

[a]Follow-up: 8 years; data reported by Baek et al. (2023); goserelin for 2 years

[b]Follow-up: 12 years; data reported by Hackshaw et al. (2009); goserelin for 2 years

Figure 21 Disease-free survival 8 to 12 years follow-up – subgroup analysis by duration of OFS –FE model



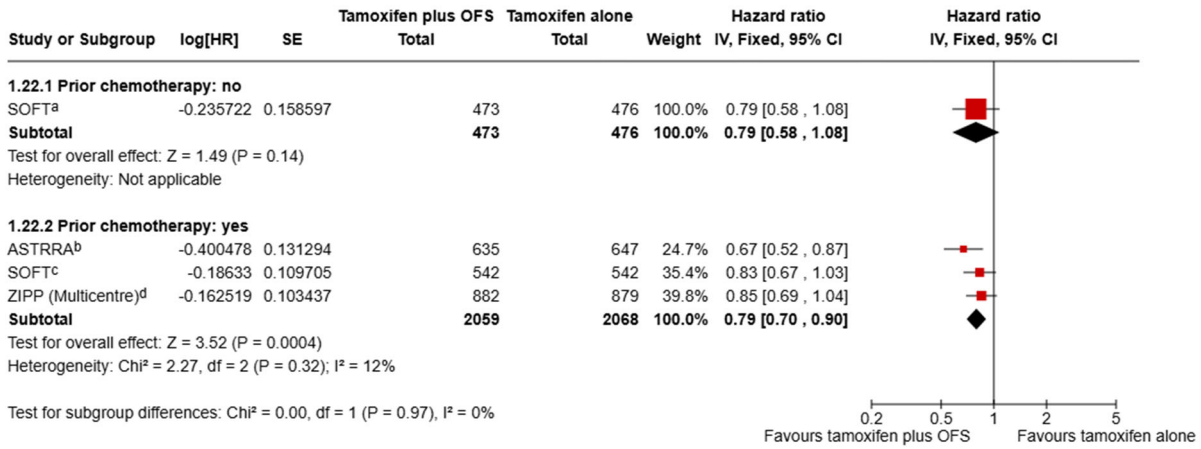
Footnotes

[a]Follow-up: 8 years; data reported by Baek et al. (2023); goserelin for 2 years

[b]Follow-up: 12 years; data reported by Hackshaw et al. (2009); goserelin for 2 years

[c]Follow-up: 12 years; data reported by Francis et al. (2023); triptorelin for 5 years

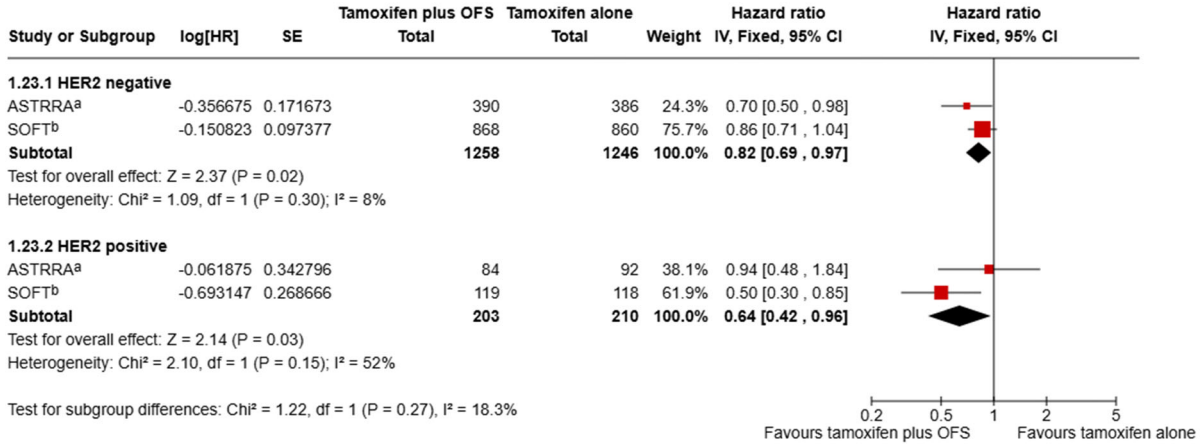
Figure 22 Disease-free survival – 8 to 12 years follow-up – subgroup analysis by use of chemotherapy



Footnotes

[a]Data reported by Francis et al. (2023); all participants without prior chemotherapy
[b]Data reported by Baek et al. (2023): all participants with prior chemotherapy
[c]Data reported by Francis et al. (2023): all participants with prior chemotherapy
[d]Data reported by Hackshaw et al. (2009): prior chemotherapy was allowed

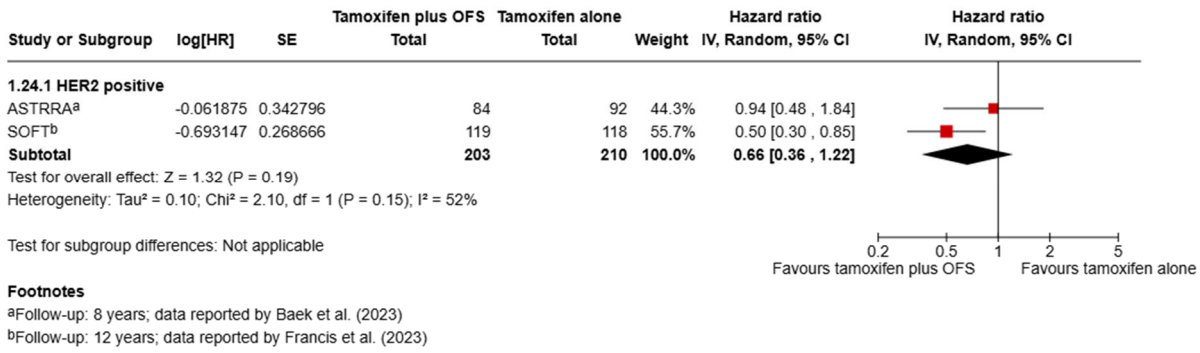
Figure 23 Disease-free survival – 12 years follow-up – subgroup analysis by HER2 status –FE model



Footnotes

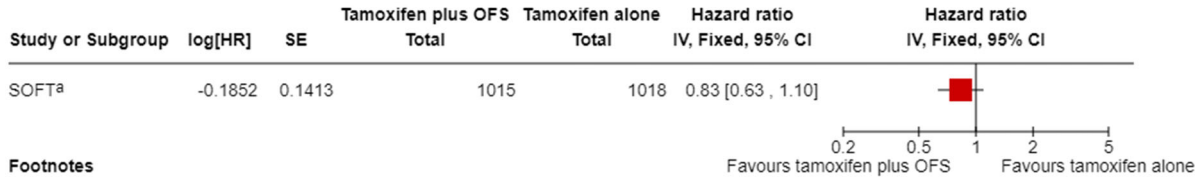
[a]Follow-up: 8 years; data reported by Baek et al. (2023)
[b]Follow-up: 12 years; data reported by Francis et al. (2023)

Figure 24 Disease-free survival – 8 to 12 years follow-up – subgroup analysis by HER2 status – RE model (I2 >50%)



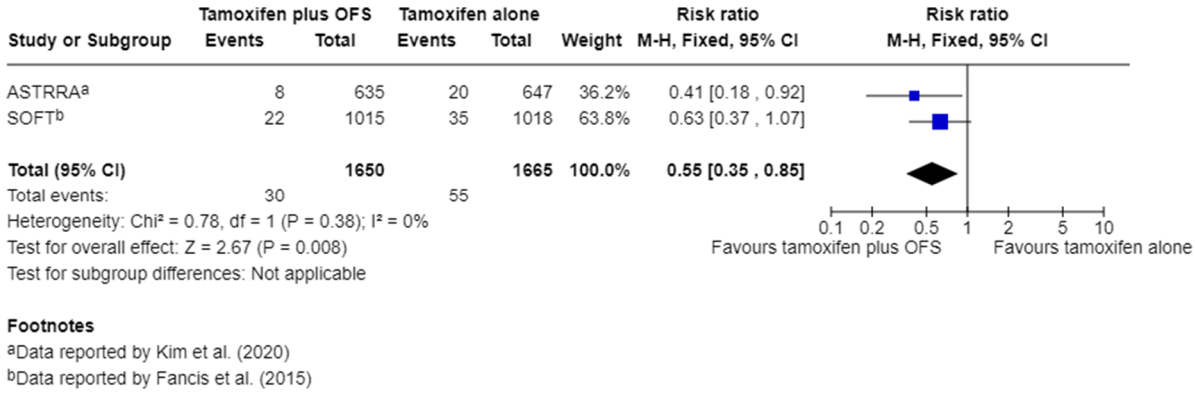
Breast cancer mortality

Figure 25 Breast cancer mortality (reported as event data for death after breast cancer event) – 12 years follow-up



Local and/or locoregional recurrence

Figure 26 Local and/or locoregional recurrence – 5 years follow-up

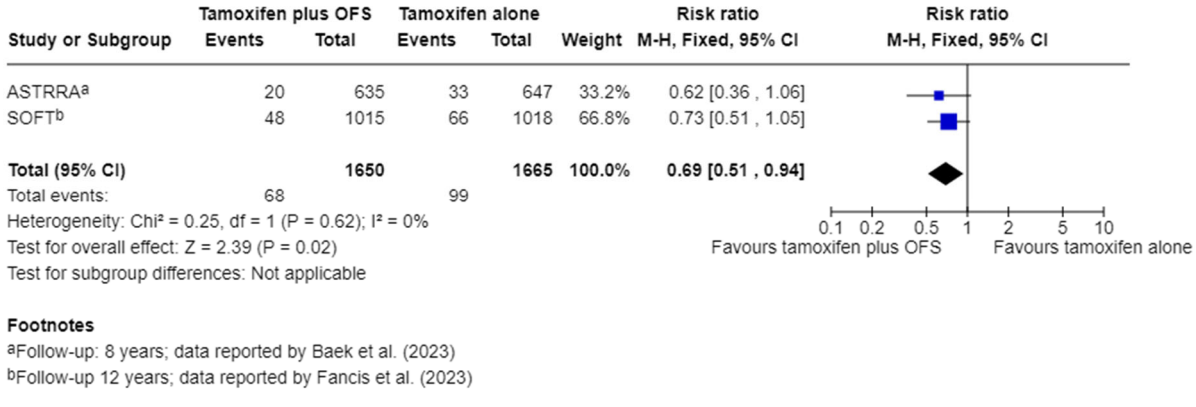


Footnotes

[a]Data reported by Kim et al. (2020)

[b]Data reported by Fancis et al. (2015)

Figure 27 Local and /or locoregional recurrence – 8 to 12 years follow-up



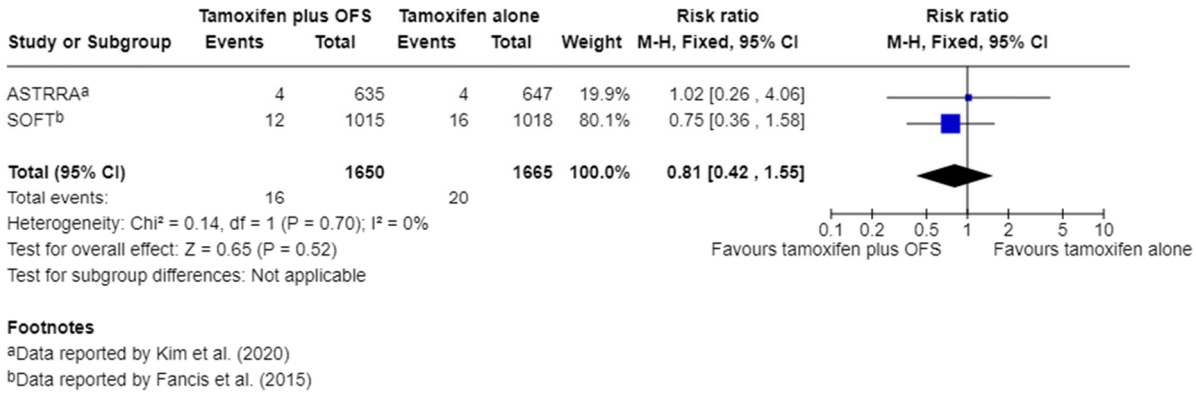
Footnotes

[a]Follow-up: 8 years; data reported by Baek et al. (2023)

[b]Follow-up 12 years; data reported by Fancis et al. (2023)

New contralateral disease

Figure 28 New contralateral disease – 5 years follow-up

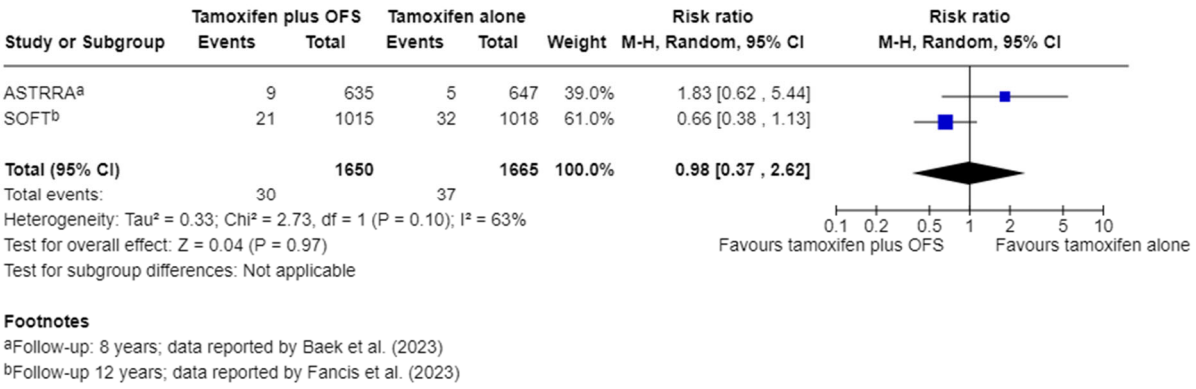


Footnotes

[a]Data reported by Kim et al. (2020)

[b]Data reported by Fancis et al. (2015)

Figure 29 New contralateral disease – 8 to 12 years follow-up



Footnotes

[a]Follow-up: 8 years; data reported by Baek et al. (2023)

[b]Follow-up 12 years; data reported by Fancis et al. (2023)

Adherence to or completion of treatment

Figure 30 Adherence to or completion of treatment (treatment completed at 5 years)

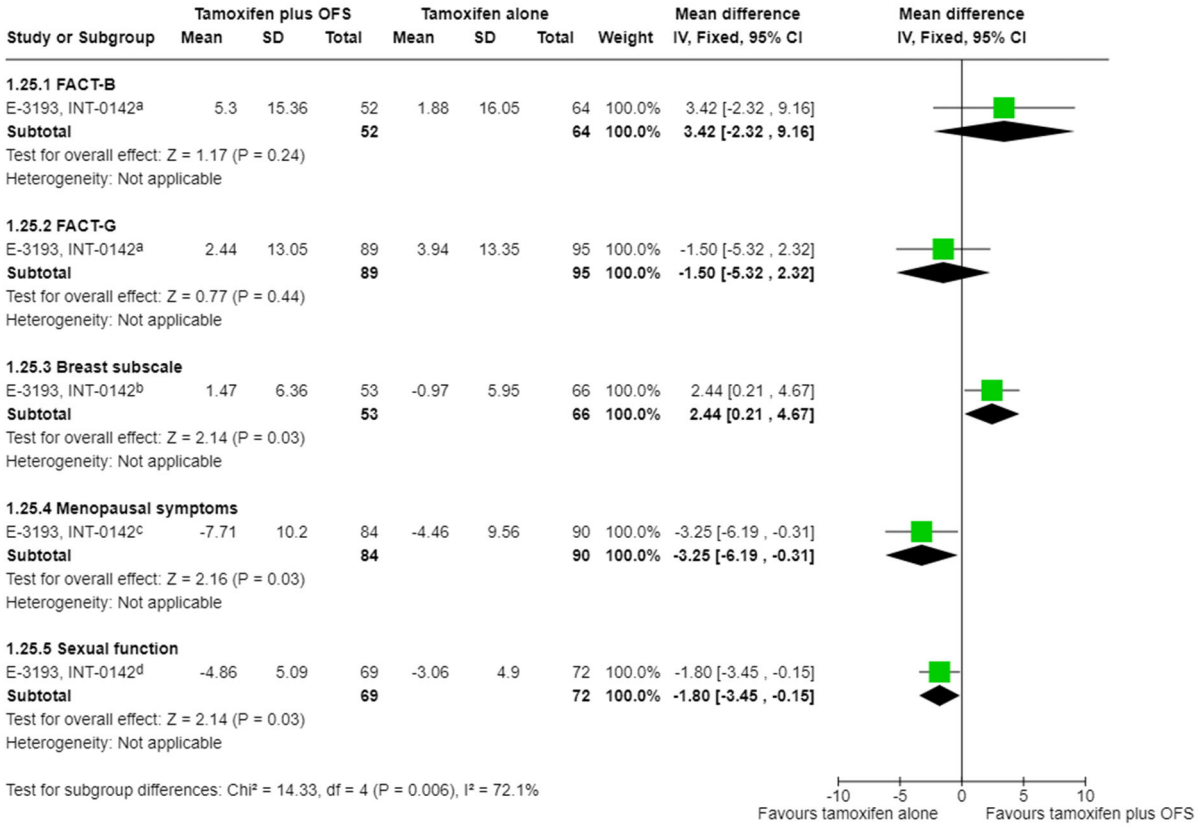
Footnotes

[a]Data reported by Tevaarwerk et al. (2014)

[b]Data reported by Francis et al. (2015); number of events calculated from percentages

Quality of life

Figure 31 Quality of life – 5 years follow-up – (higher scores indicate better quality of life)



Footnotes

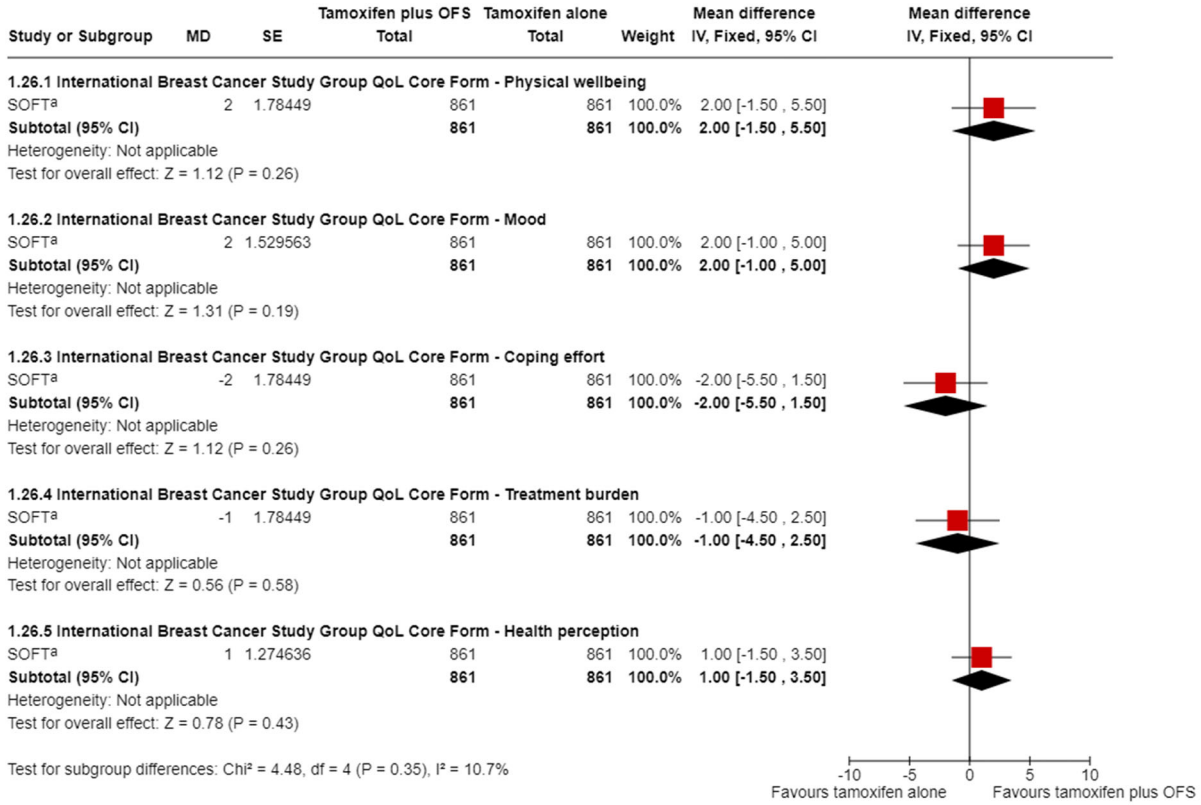
[a]Data reported by Tevaarwerk et al. (2014); changes from baseline; higher scores indicate better quality of life

[b]Data reported by Tevaarwerk et al. (2014); changes from baseline; higher scores indicate fewer breast cancer specific symptoms

[c]Data reported by Tevaarwerk et al. (2014); changes from baseline; higher scores indicate fewer complaints or difficulty

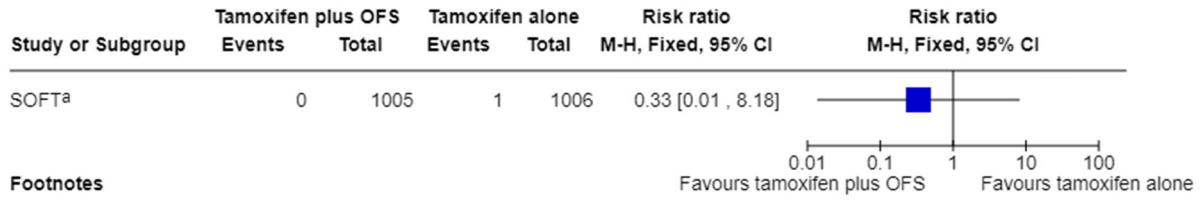
[d]Data reported by Tevaarwerk et al. (2014); changes from baseline; higher scores indicates better sexual activity

Figure 32 Quality of life – 5 years follow-up – (higher scores indicate better quality of life)



Treatment-related mortality

Figure 33 adverse events - cardiovascular – cardiac ischaemia or infarction (grades 5; treatment-related mortality)



Adverse events

Figure 34 Adverse events – genitourinary: vaginal dryness

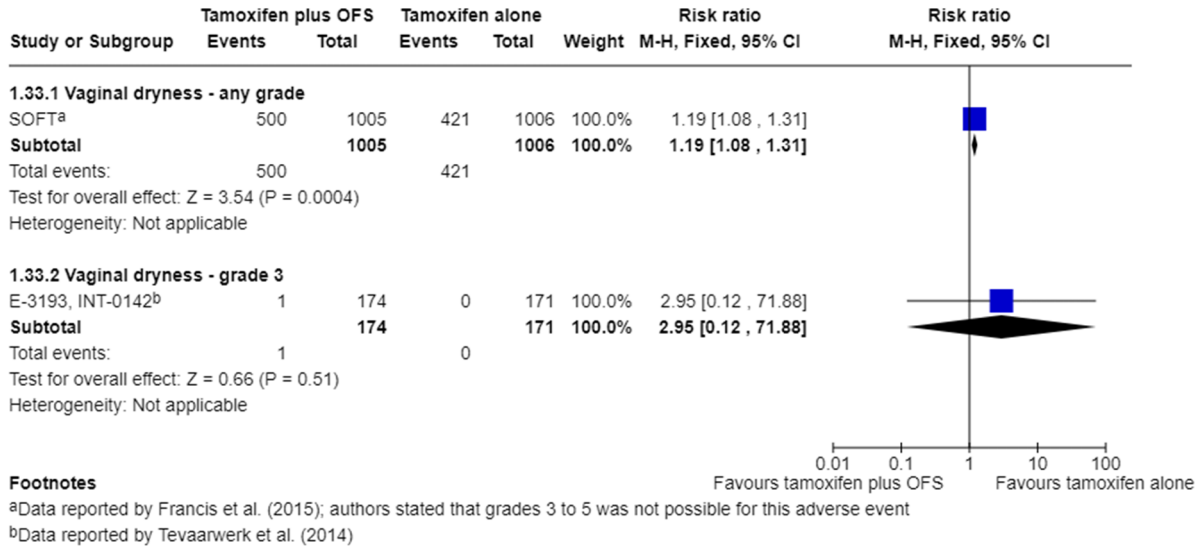


Figure 35 Adverse events – genitourinary: incontinence

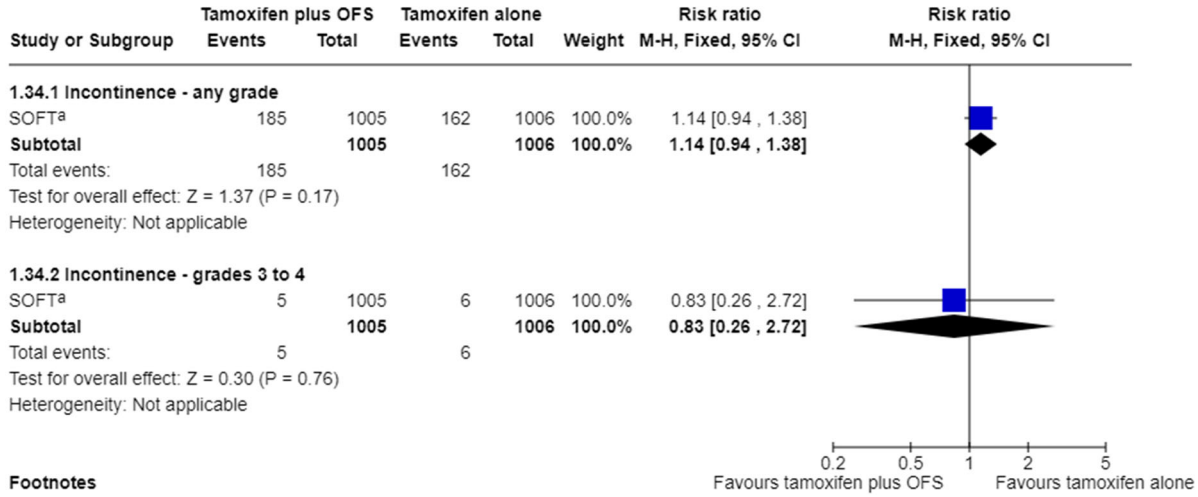
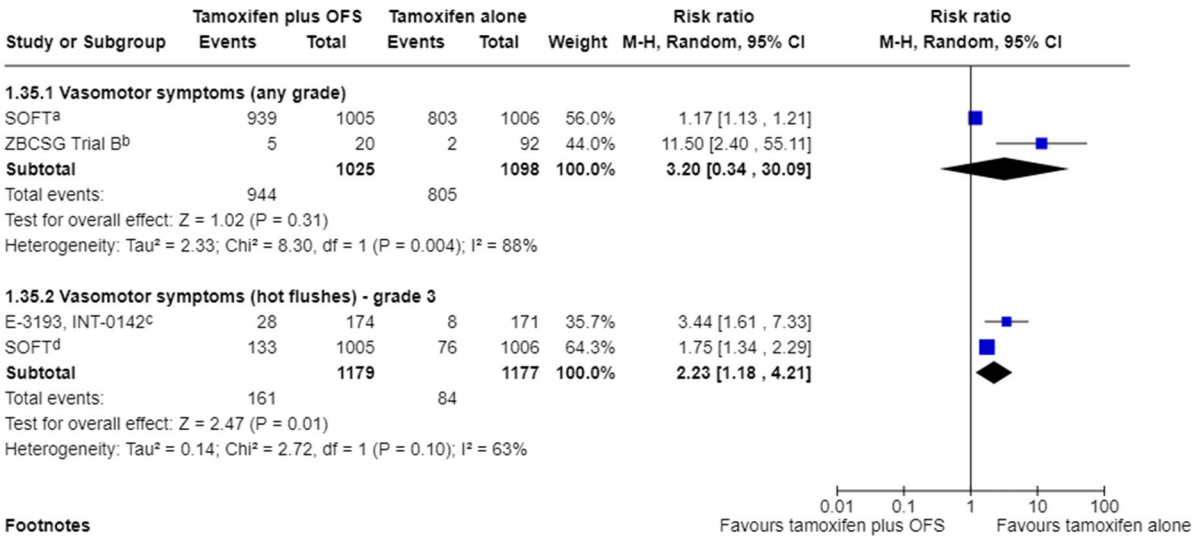


Figure 36 Adverse events – menopausal symptoms: vasomotor symptoms



Footnotes

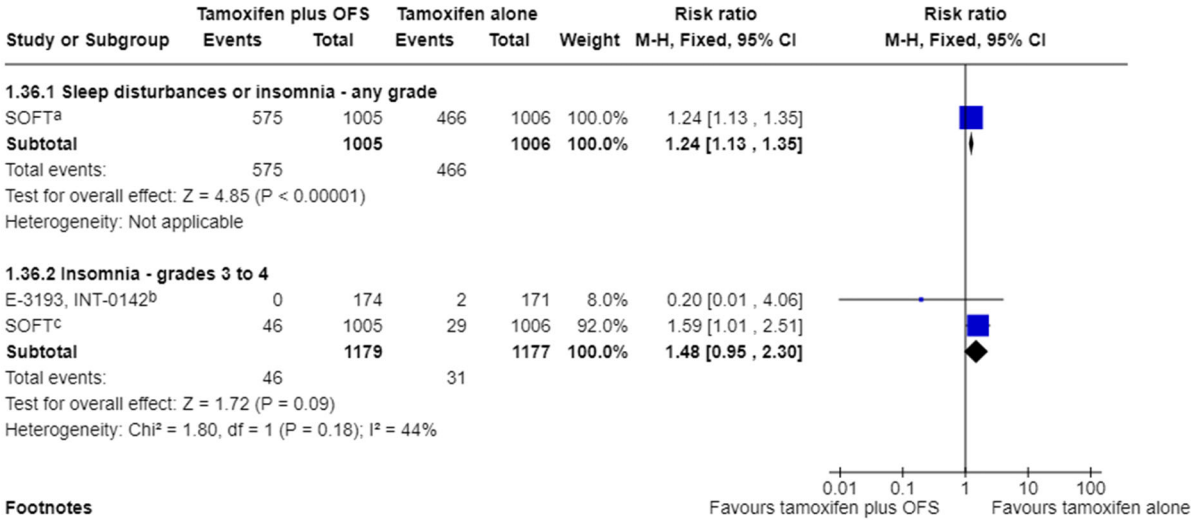
[a]Data reported by Francis et al. (2015). Hot flushes symptom reported only to avoid double counting

[b]Data reported by Bui et al. (2020) for the symptom hot flushes

[c]Data reported by Tevaarwerk et al. (2014)

[d]Data reported by Francis et al. (2015)

Figure 37 Adverse events – menopausal symptoms – sleep disturbances



Footnotes

[a]Data reported by Francis et al. (2015) for insomnia

[b]Data reported by Tevaarwerk et al. (2014)

[c]Data reported by Francis et al. (2015)

Figure 38 Adverse events – menopausal symptoms: fatigue

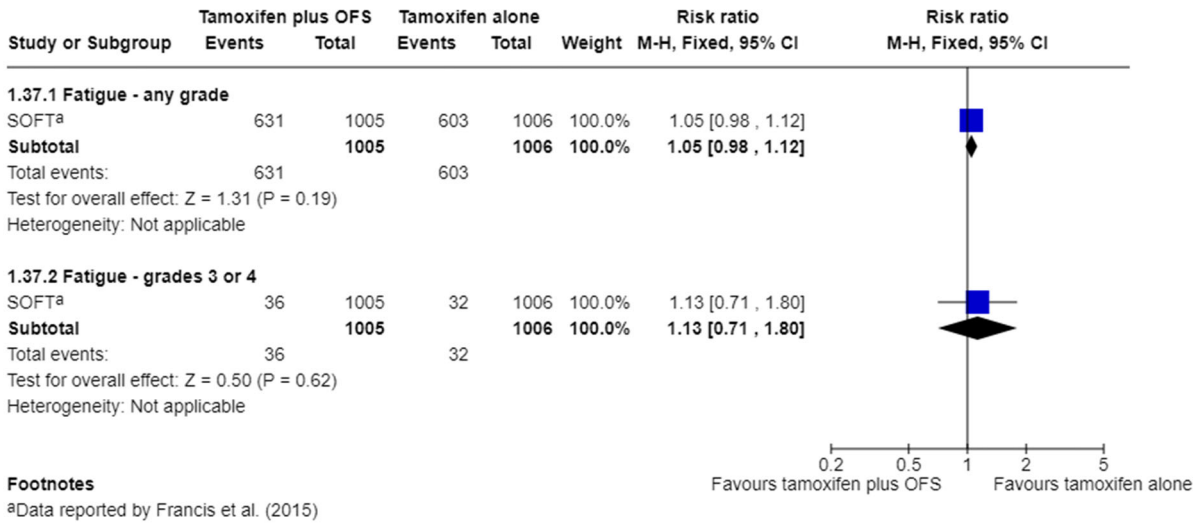


Figure 39 Adverse events – menopausal symptoms: weight gain

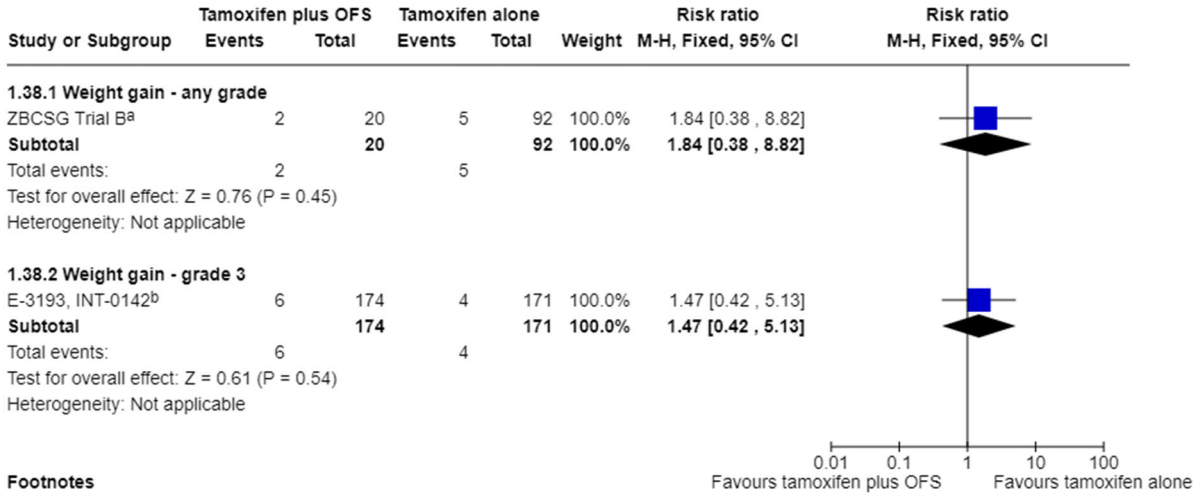
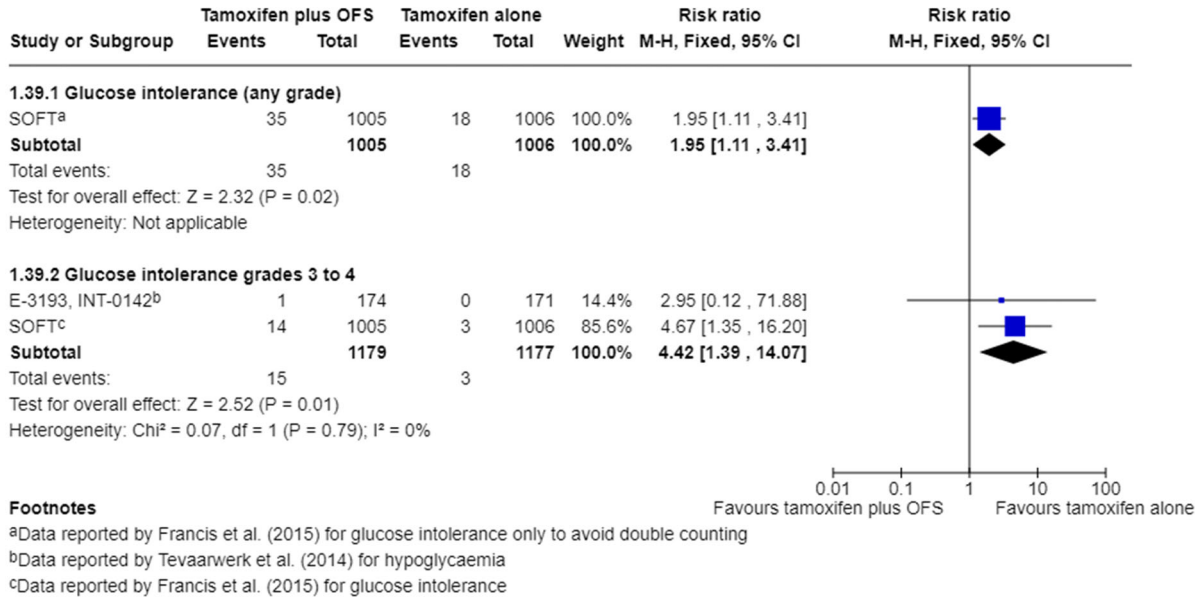


Figure 40 Adverse events – glucose intolerance



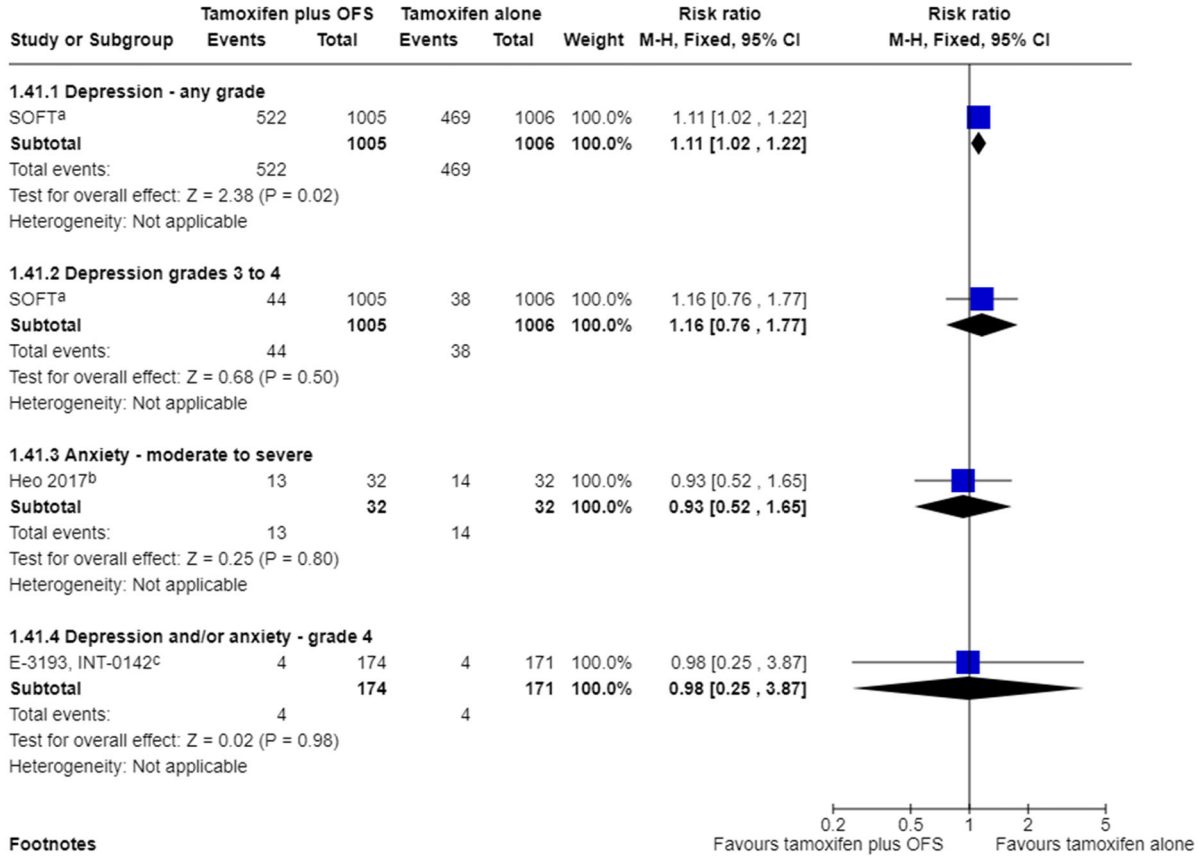
Footnotes

[a]Data reported by Francis et al. (2015) for glucose intolerance only to avoid double counting

[b]Data reported by Tevaarwerk et al. (2014) for hypoglycaemia

[c]Data reported by Francis et al. (2015) for glucose intolerance

Figure 41 Adverse events – neurocognitive: depression and/ or anxiety



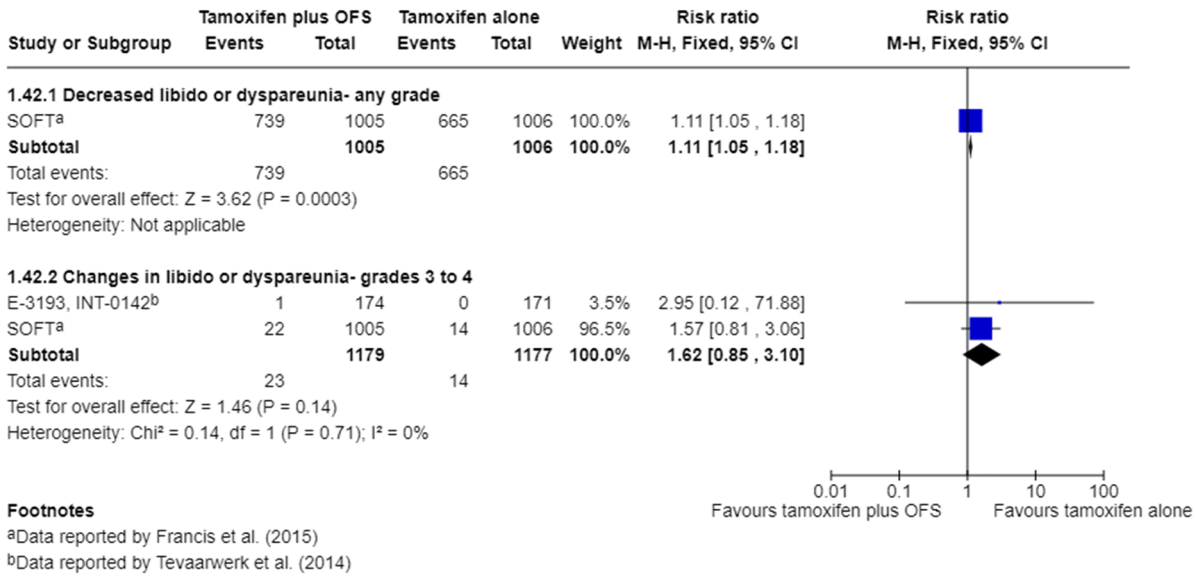
Footnotes

[a]Data reported by Francis et al. (2015)

[b]Data reported by Bui et al. (2020)

[c]Data reported by Tevaarwerk et al. (2014). Reported as neuropsychiatric symptoms including anxiety and depression

Figure 42 Adverse events – psychosexual: sexual function

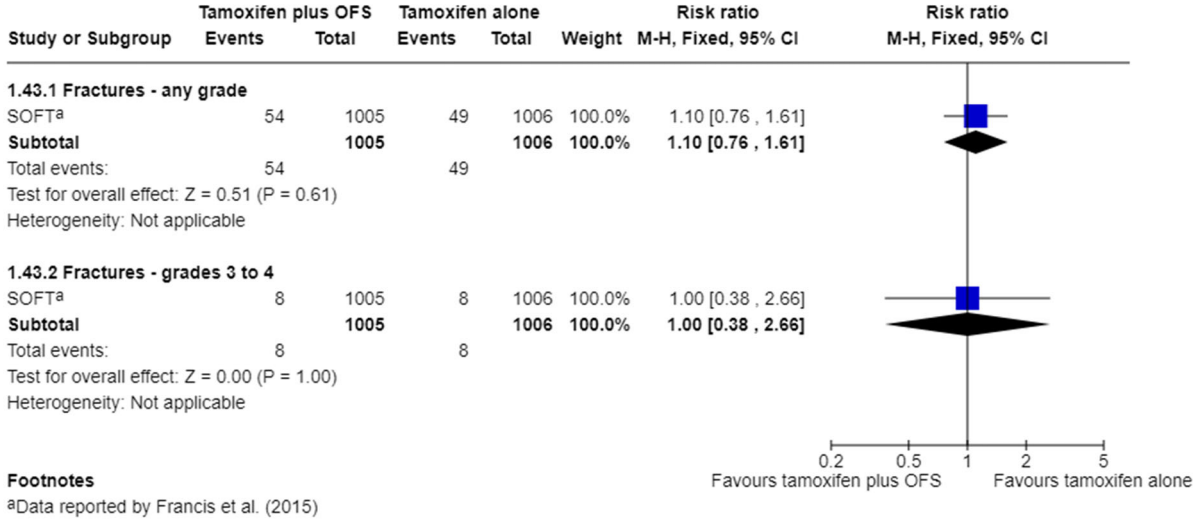


Footnotes

[a]Data reported by Francis et al. (2015)

[b]Data reported by Tevaarwerk et al. (2014)

Figure 43 Adverse events – musculoskeletal: fracture



Footnotes

[a]Data reported by Francis et al. (2015)

Figure 44 Adverse events – musculoskeletal: osteoporosis

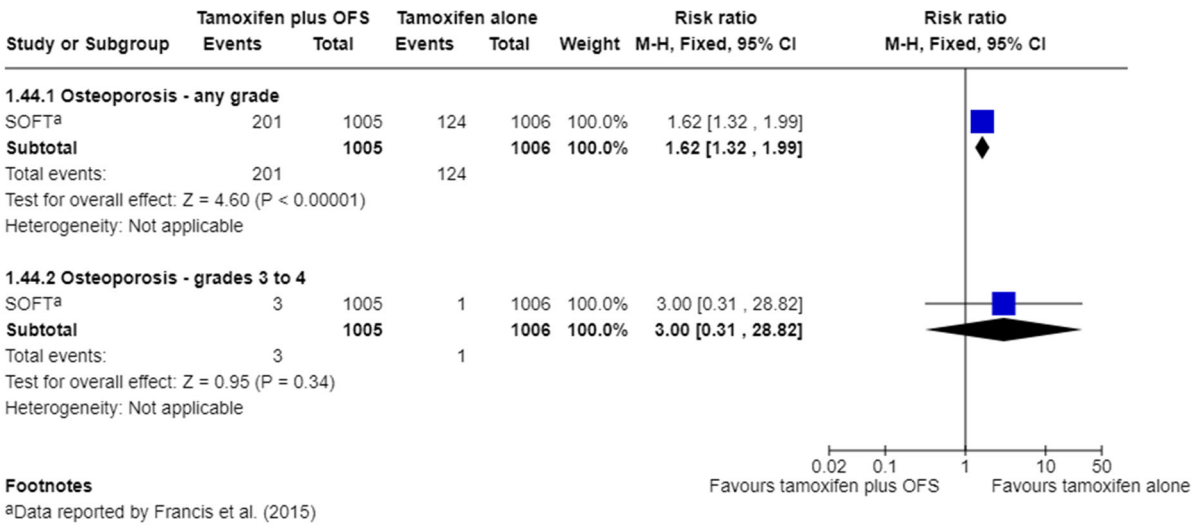


Figure 45 Adverse events - cardiovascular – thrombosis or embolism (grades 3 or 4)

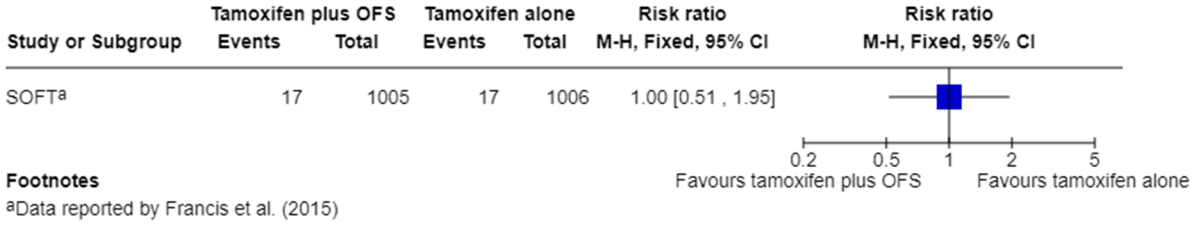
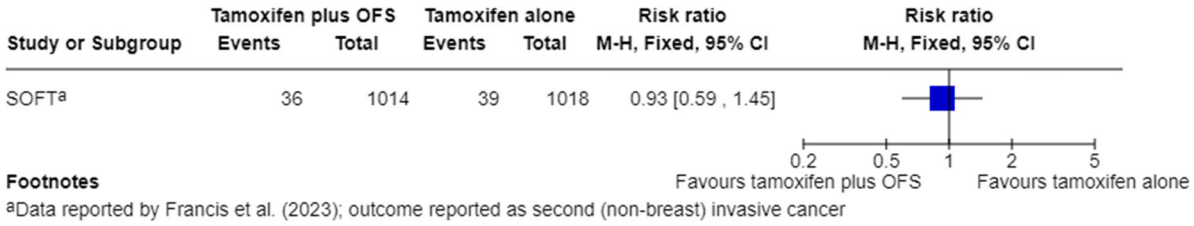


Figure 46 Adverse events – cardiovascular – cardiac ischaemia or infarction (grades 3 or 4)

Figure 47 adverse events - other cancers



Ovarian function suppression combined with an aromatase inhibitor compared to tamoxifen alone

Overall survival

Figure 48 Overall survival – 5 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)

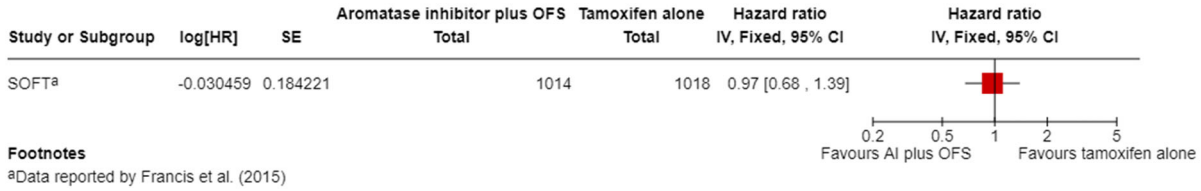


Figure 49 Overall survival – 5 years follow-up – subgroup analysis by prior use of chemotherapy

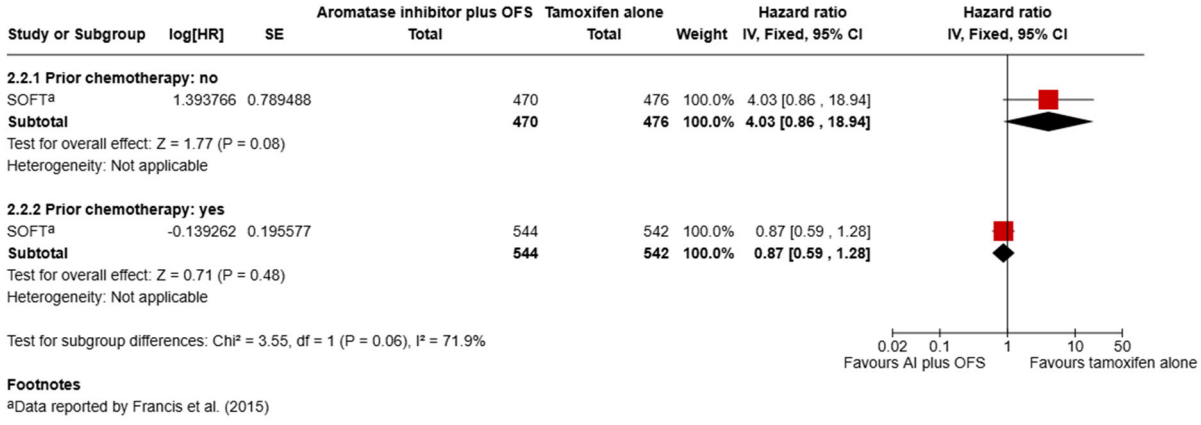
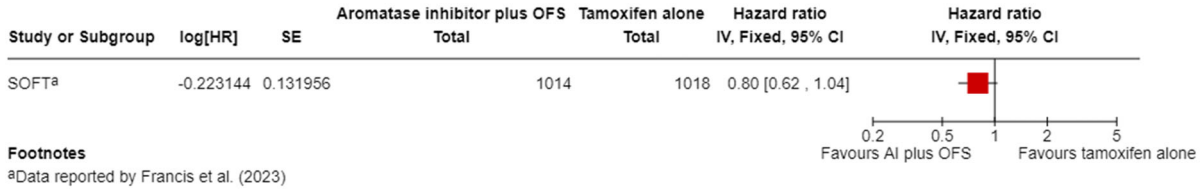


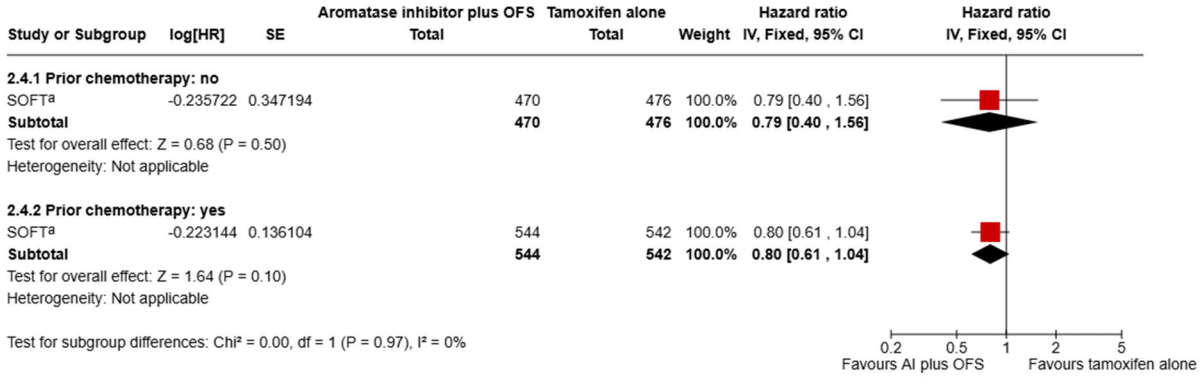
Figure 50 Overall survival – 12 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)



Footnotes

[a]Data reported by Francis et al. (2023)

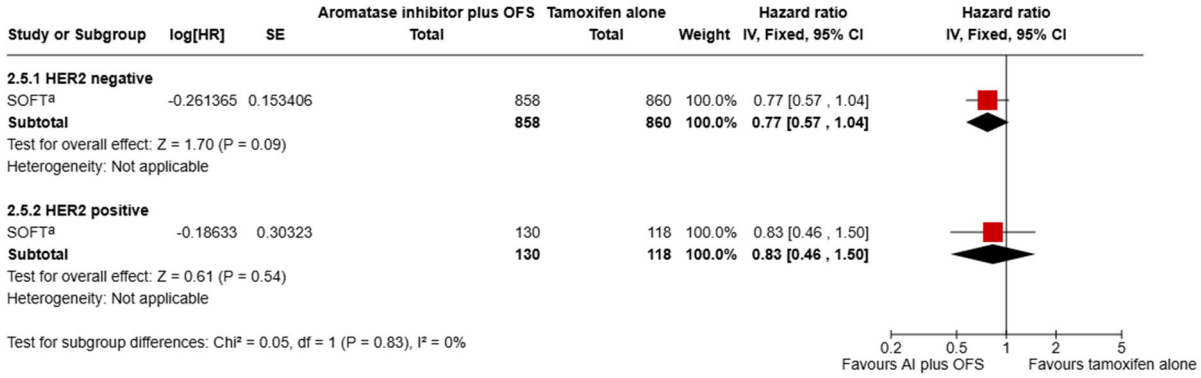
Figure 51 Overall survival – 12 years follow-up – subgroup analysis by prior use of chemotherapy



Footnotes

[a]Data reported by Francis et al. (2023)

Figure 52 Overall survival – 12 years follow-up – subgroup analysis by HER2 status

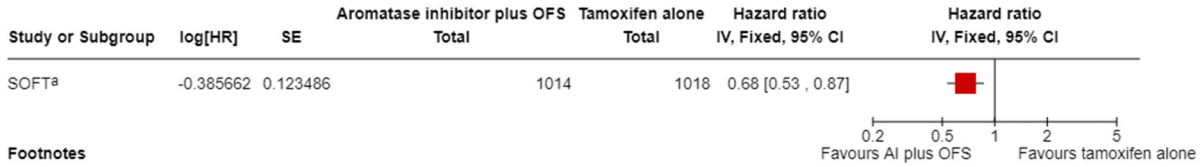


Footnotes

[a]Data reported by Francis et al. (2023)

Disease-free survival

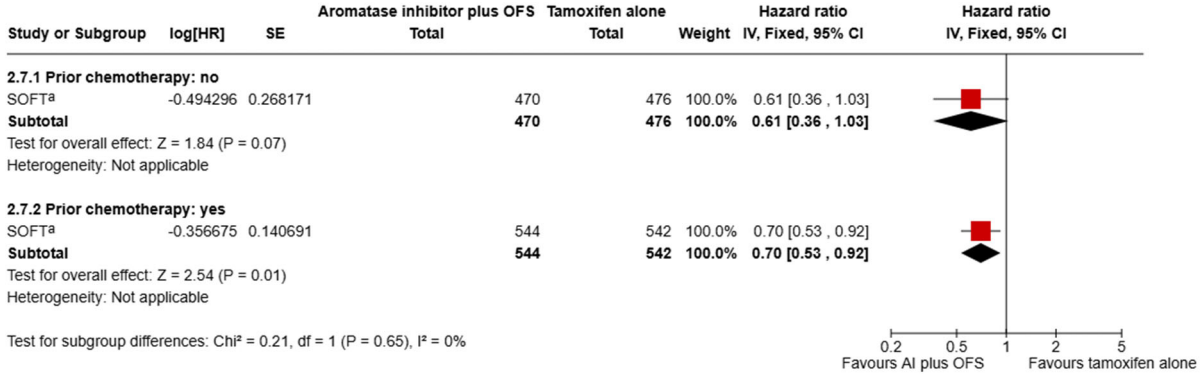
Figure 53 Disease-free survival – 5 years follow-up – (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone)



Footnotes

[a]Data reported by Francis et al. (2015)

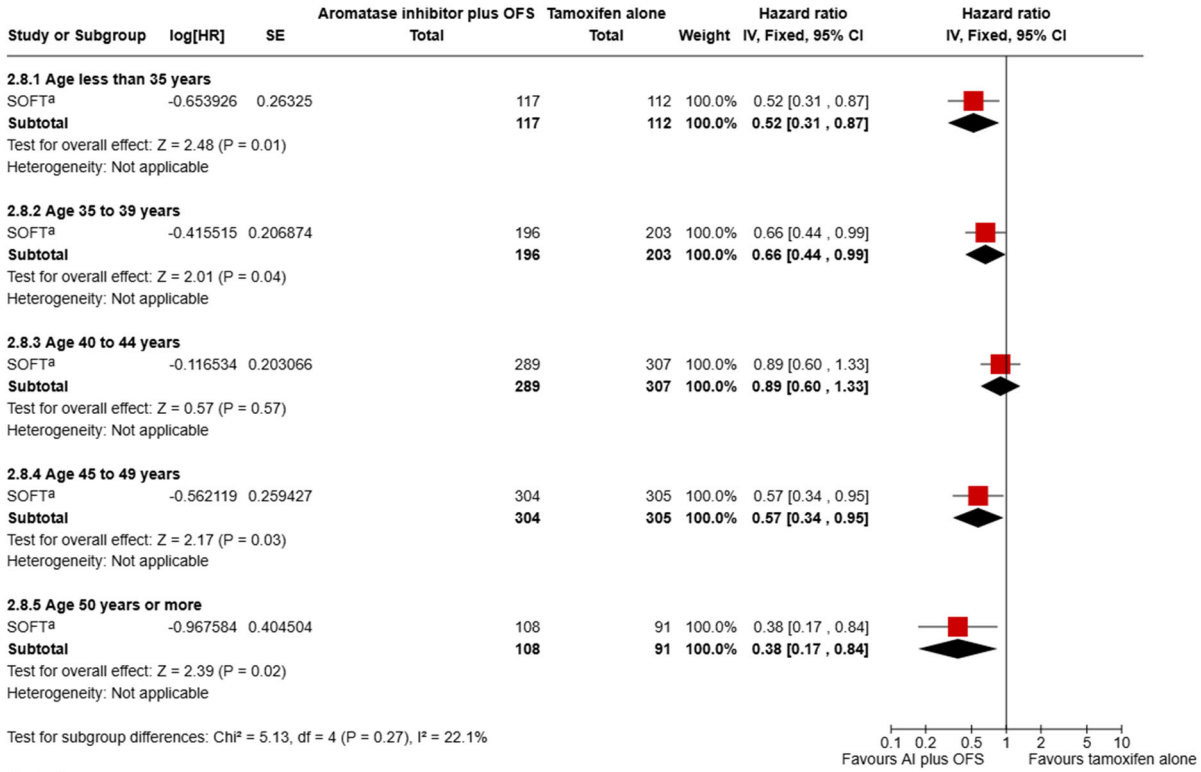
Figure 54 Disease-free survival – 5 years follow-up – subgroup analysis by prior use of chemotherapy



Footnotes

[a]Data reported by Francis et al. (2015)

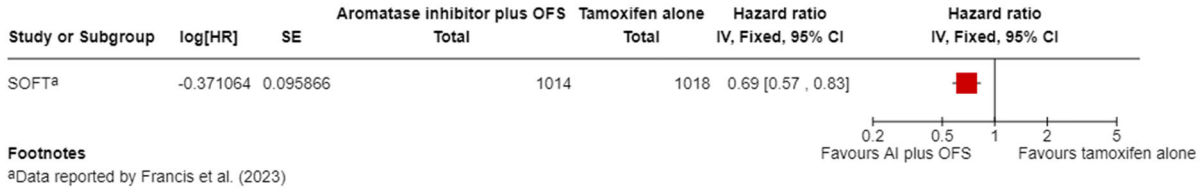
Figure 55 Disease-free survival – 8 years follow-up – subgroup analysis by age



Footnotes

[a]Data reported by Francis et al. (2018)

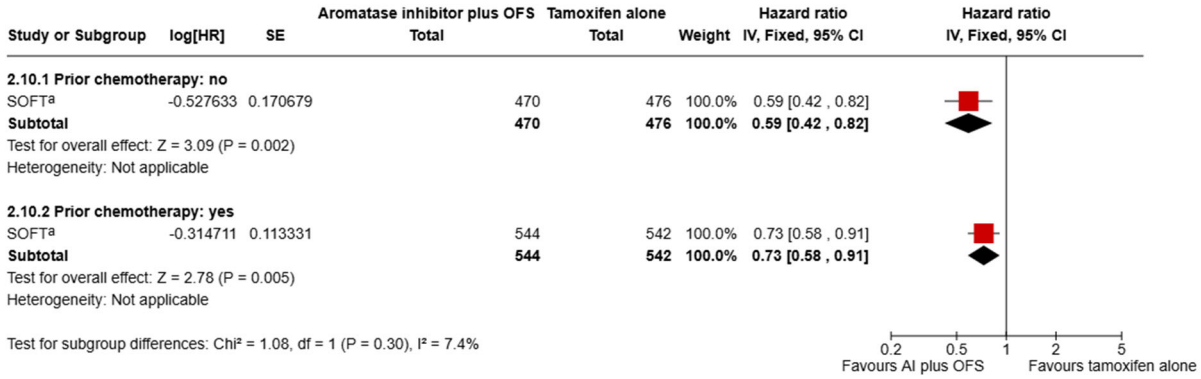
Figure 56 Disease-free survival – 12 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)



Footnotes

[a]Data reported by Francis et al. (2023)

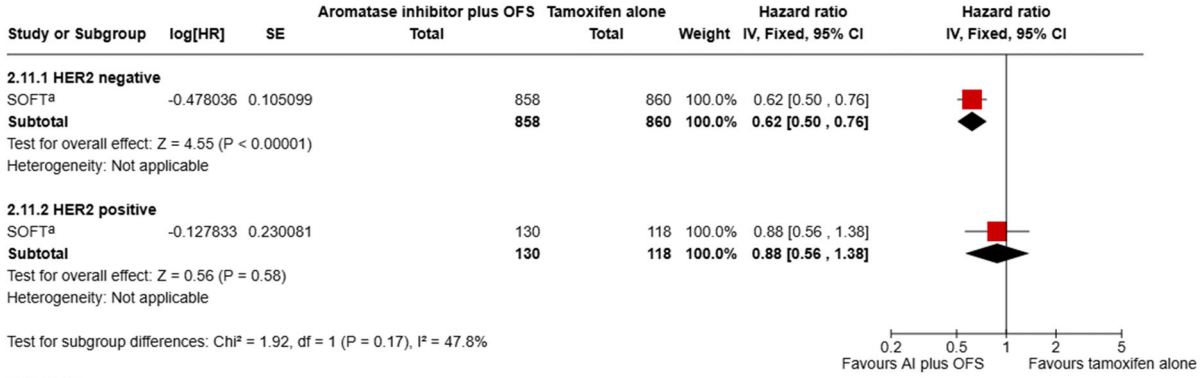
Figure 57 Disease-free survival – 12 years follow-up – subgroup analysis by prior use of chemotherapy



Footnotes

[a]Data reported by Francis et al. (2023)

Figure 58 Disease-free survival – 12 years follow-up – subgroup analysis by HER2 status

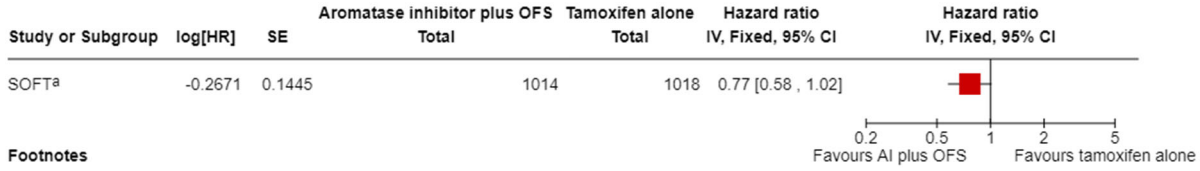


Footnotes

[a]Data reported by Francis et al. (2023)

Breast cancer mortality

Figure 59 Breast cancer mortality (reported as event data for death after breast cancer event) – 12 years follow-up

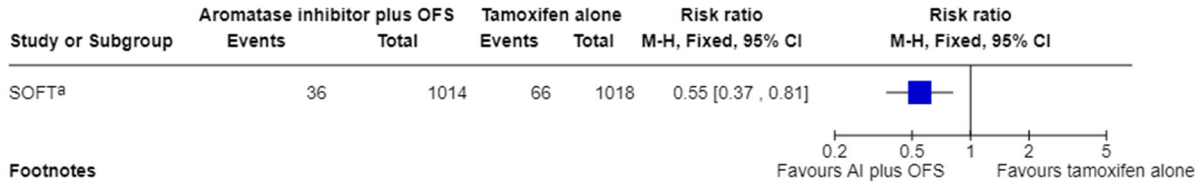


Footnotes

[a]Data reported by Francis et al. (2023); log HR and standard error of HR were calculated using number of events and total sample

Local and/or locoregional recurrence

Figure 60 Local and/or locoregional recurrence – 12 years follow-up

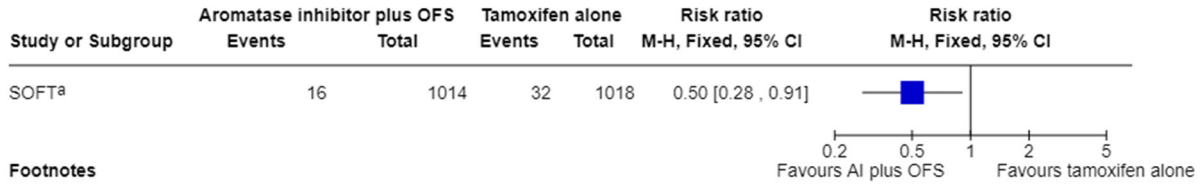


Footnotes

[a]Data reported by Francis et al. (2023)

New contralateral disease

Figure 61 New contralateral disease – 12 years follow-up



Footnotes

[a]Data reported by Francis et al. (2023)

Adherence to or completion of treatment

Figure 62 Adherence to or completion of treatment (treatment completed at 8 years)

Footnotes

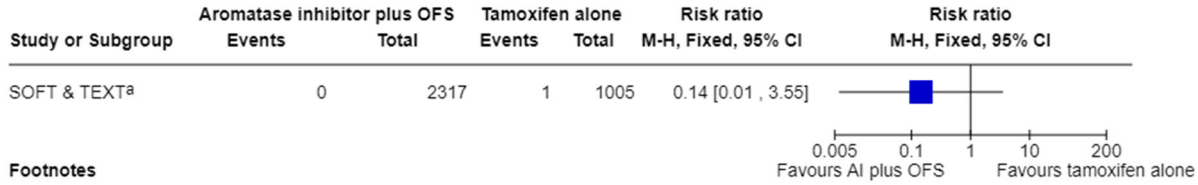
[a]Data reported by Francis et al. (2018)

Quality of life

No evidence for this outcome

Treatment-related mortality

Figure 63 Adverse events – cardiovascular: cardiac ischaemia or infarction (grades 5; treatment-related mortality)



Footnotes

[a]Data reported by Francis et al. (2018)

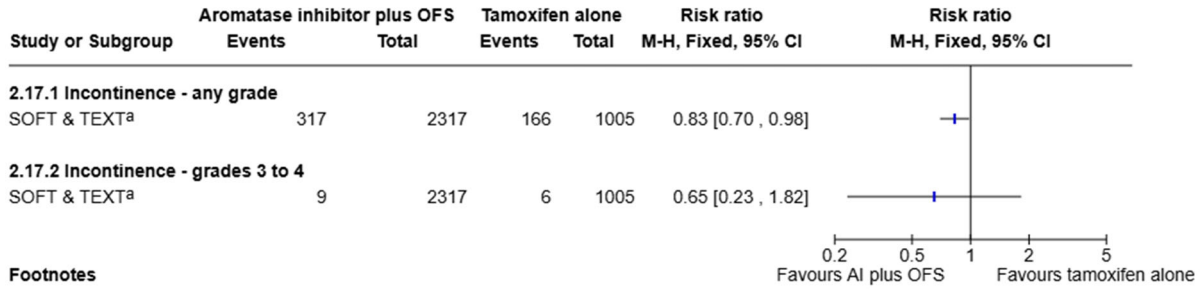
Adverse events

Figure 64 Adverse events – genitourinary: vaginal dryness (any grade)

Footnotes

[a]Data reported by Francis et al. (2018)

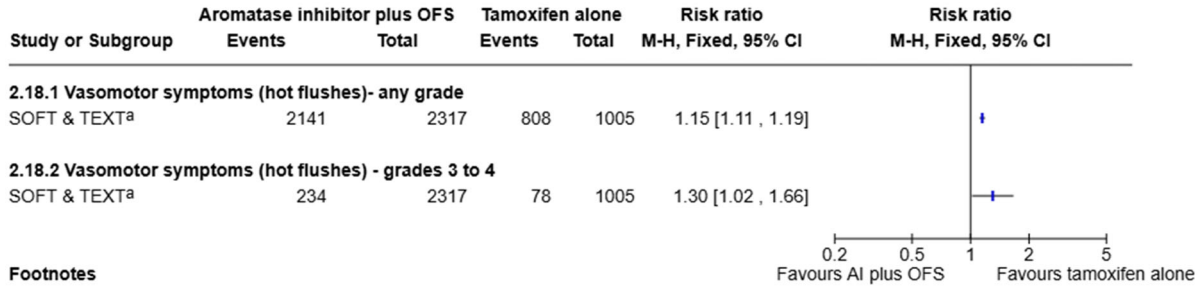
Figure 65 adverse events – genitourinary: incontinence



Footnotes

[a]Data reported by Francis et al. (2018)

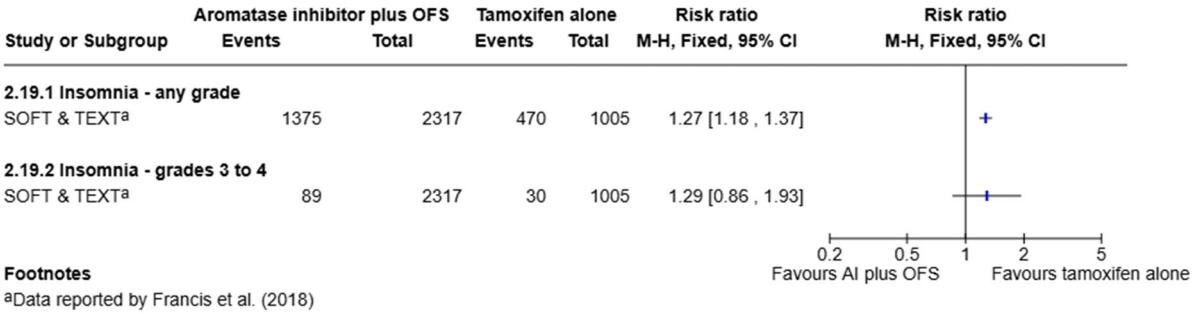
Figure 66 Adverse events – menopausal symptoms: vasomotor symptoms



Footnotes

[a]Data reported by Francis et al. (2018) Hot flushes symptom reported only to avoid double counting

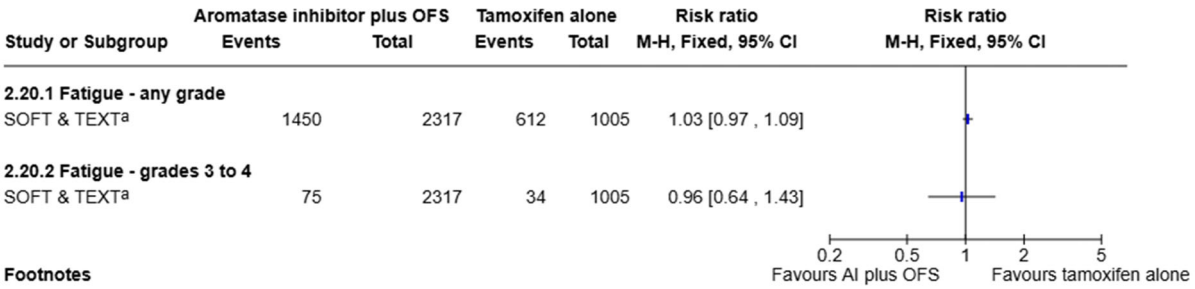
Figure 67 Adverse events – menopausal symptoms: sleep disturbances



Footnotes

[a]Data reported by Francis et al. (2018)

Figure 68 Adverse events - menopausal symptoms: fatigue



Footnotes

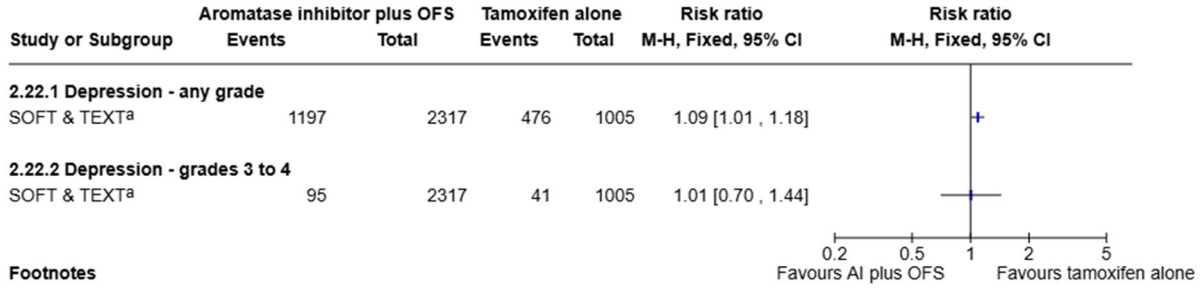
[a]Data reported by Francis et al. (2018)

Figure 69 Adverse events – glucose intolerance

Footnotes

[a]Data reported by Francis et al. (2018). Only glucose intolerance outcome from this study reported to avoid double counting

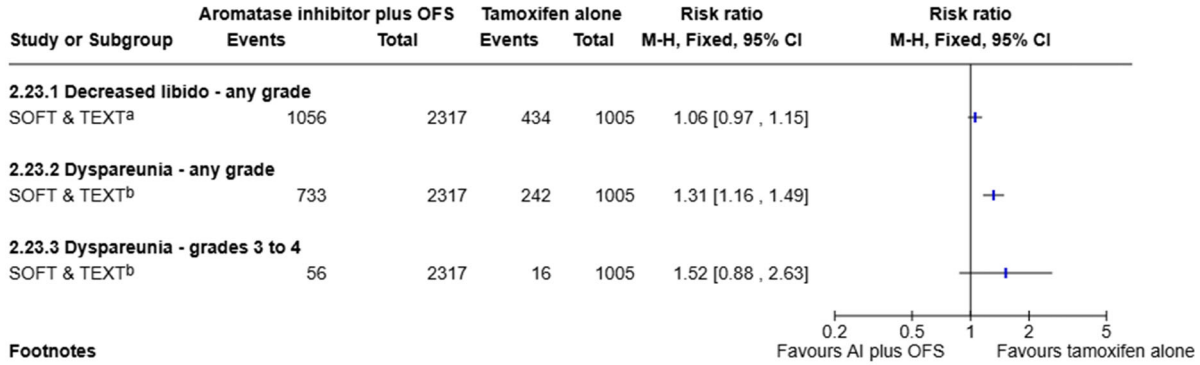
Figure 70 Adverse events – neurocognitive – depression (any grade)



Footnotes

[a]Data reported by Francis et al. (2018)

Figure 71 Adverse events – psychosexual: sexual function

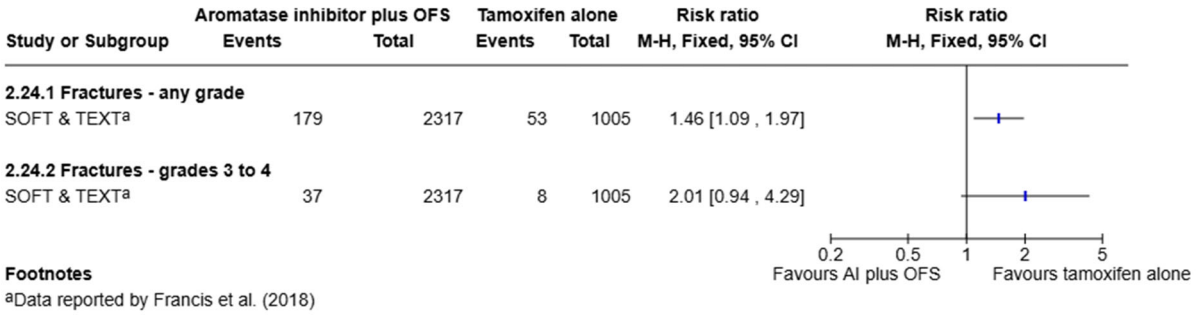


Footnotes

[a]Data reported by Francis et al. (2018). Authors stated that grades 3 or 4 were not applicable for decreased libido

[b]Data reported by Francis et al. (2018)

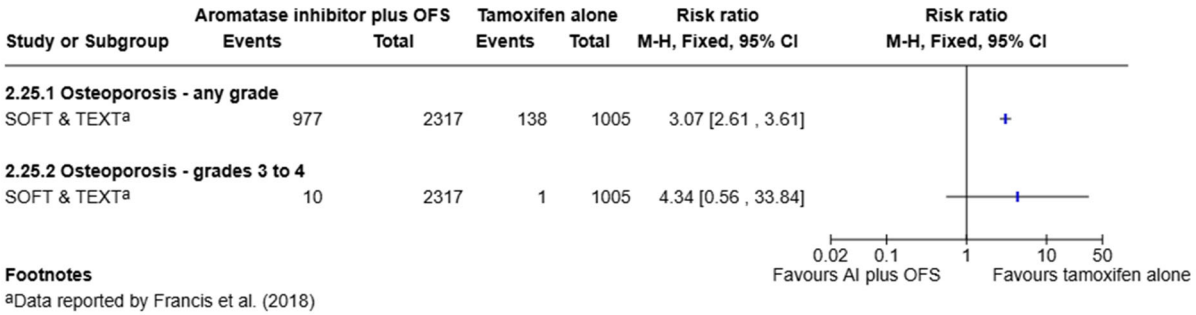
Figure 72 Adverse events – musculoskeletal: fractures



Footnotes

[a]Data reported by Francis et al. (2018)

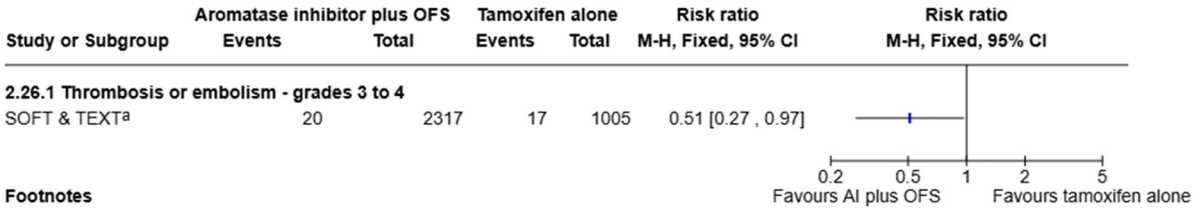
Figure 73 Adverse events – musculoskeletal: osteoporosis



Footnotes

[a]Data reported by Francis et al. (2018)

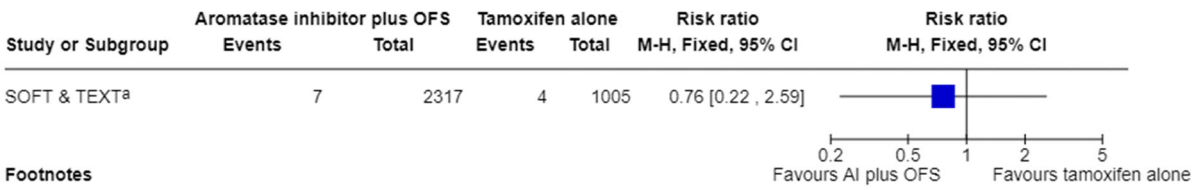
Figure 74 Adverse events – cardiovascular: thrombosis or embolism



Footnotes

[a]Data reported by Francis et al. (2018)

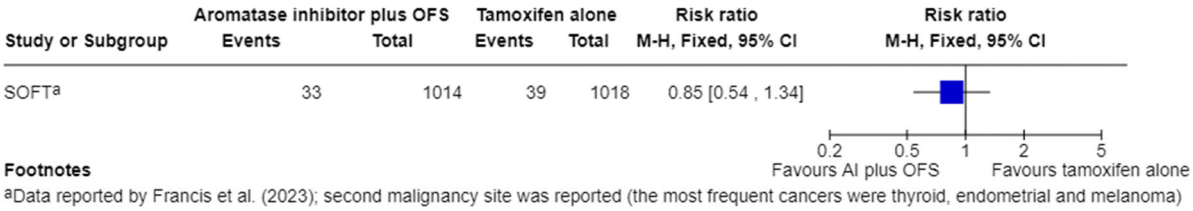
Figure 75 Adverse events – cardiovascular: cardiac ischaemia or infarction (grades 3 or more)



Footnotes

[a]Data reported by Francis et al. (2018)

Figure 76 Adverse events – other cancers



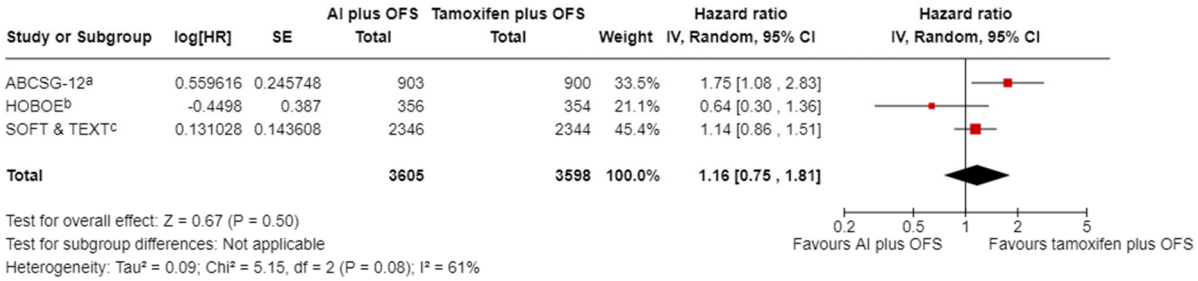
Footnotes

[a]Data reported by Francis et al. (2023); second malignancy site was reported (the most frequent cancers were thyroid, endometrial and melanoma)

Ovarian function suppression combined with aromatase inhibitor compared to ovarian function suppression combine with tamoxifen

Overall survival

Figure 77 Overall survival – 5 years follow-up (all with method of OFS: luteinising -hormone releasing hormone agonists)



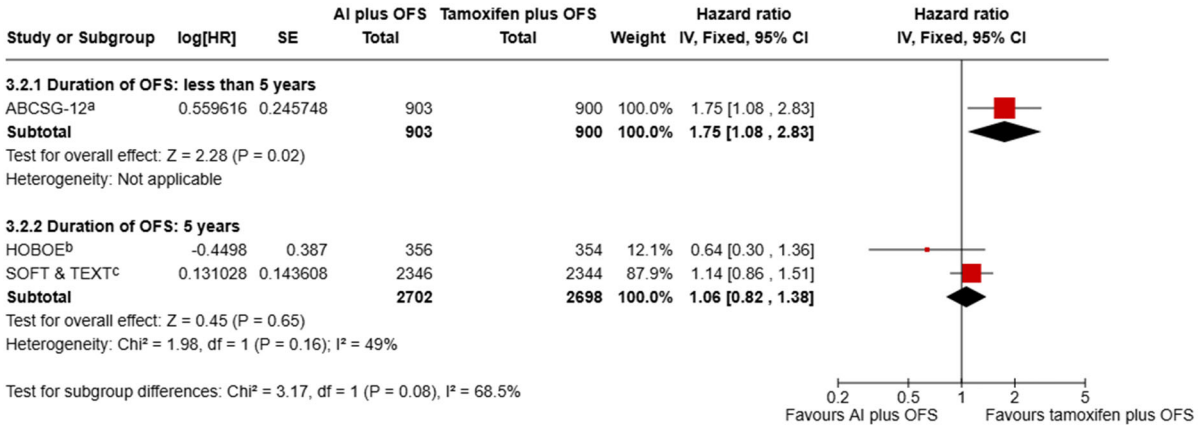
Footnotes

[a]Follow-up: 5 years; data reported by Gnant et al. (2011)

[b]Follow-up: 5 years; data reported by Perrone et al. (2019); log HR and SE of HR calculated using number of events and total sample

[c]Follow-up: 5 years; data reported by Pagani et al. (2014)

Figure 78 Overall survival – 5 years follow-up – subgroup analysis by duration of OFS



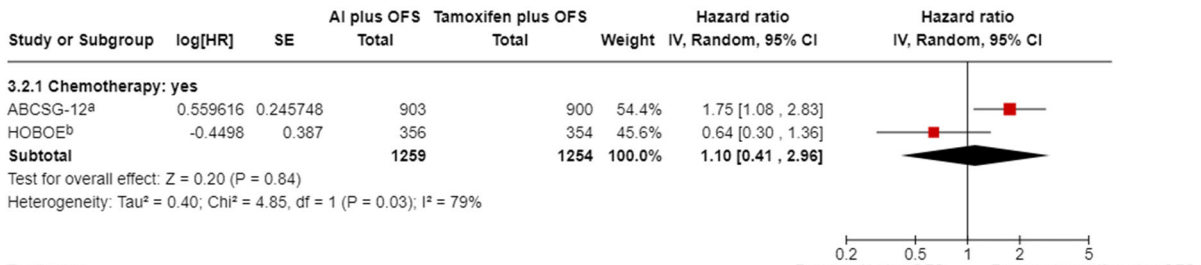
Footnotes

[a]Data reported by Gnant et al. (2011); goserelin for 3 years

[b]Data reported by Perrone et al. (2019); log HR and SE of HR calculated using number of events and total sample; triptorelin for 5 years

[c]Data reported by Pagani et al. (2014); triptorelin for 5 years

Figure 79 Overall survival – 5 years follow-up – subgroup analysis by use of chemotherapy



SOFT and TEXT were not included because they did not report data for this comparison for participants who had/ did not have chemotherapy.

Figure 80 Overall survival – 8 to 12 years follow-up (all with method of OFS: luteinising-hormone releasing hormone agonists)

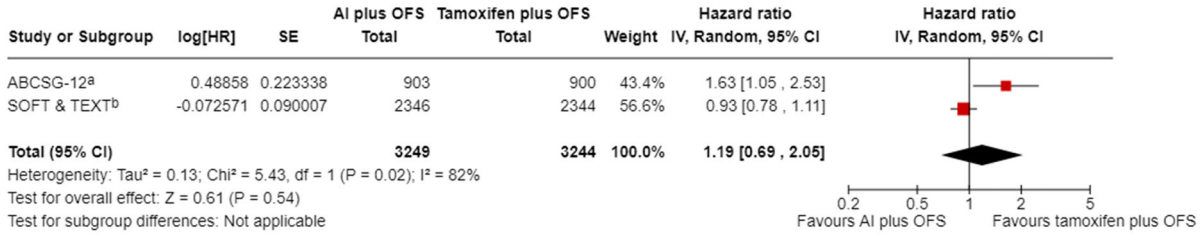


Figure 81 Overall survival – 8 to 12 years follow-up sensitivity analysis without study with concurrent chemotherapy group from TEXT study

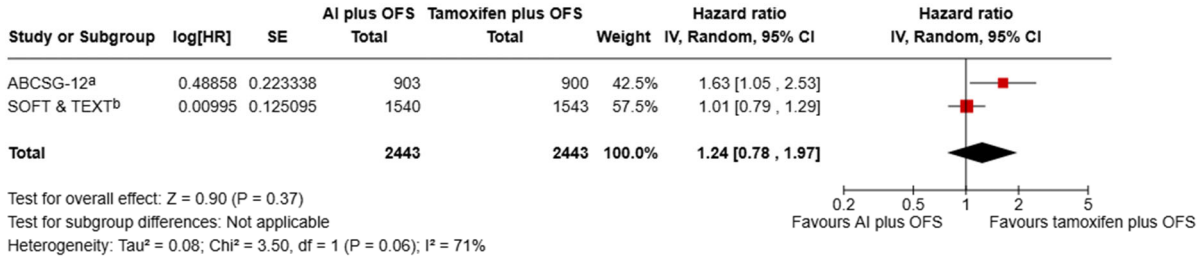
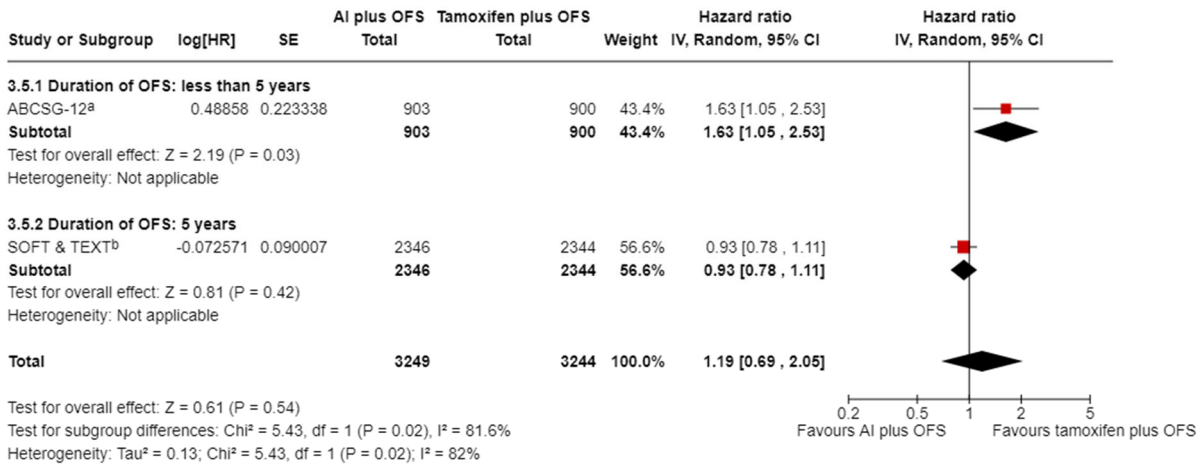


Figure 82 Overall survival – 8 to 12 years follow-up – subgroup analysis by duration of OFS

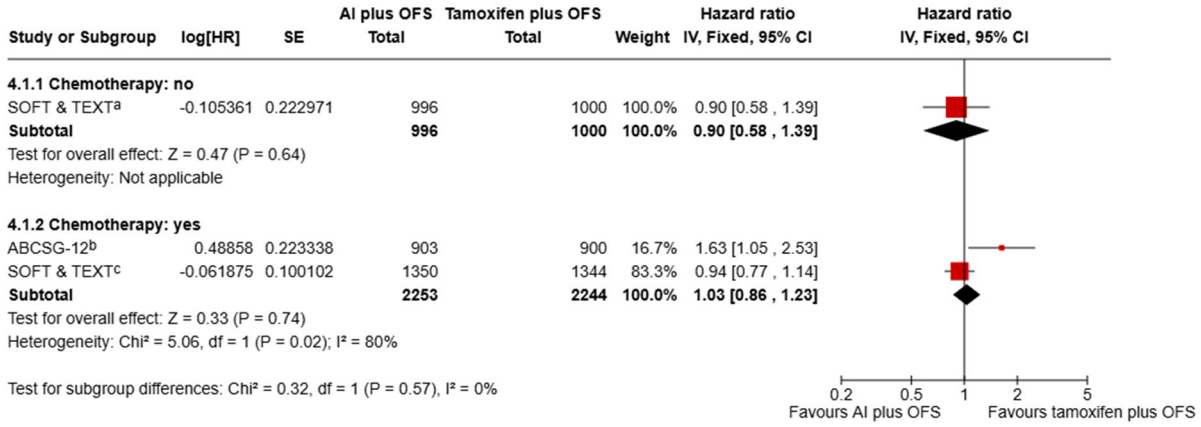


Footnotes

[a]Follow-up: 8 years; data reported by Gnant et al. (2015)

[b]Follow-up: 12 years; data reported by Pagani et al. (2022)

Figure 83 Overall survival – 8 to 12 years follow-up – subgroup analysis by use of chemotherapy – FE model



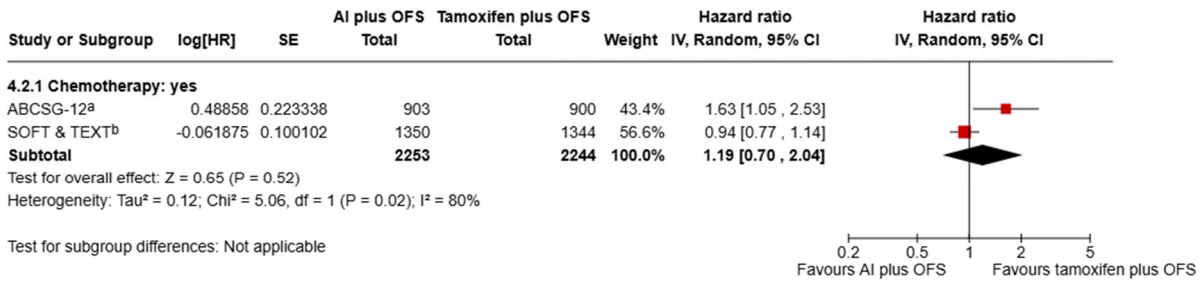
Footnotes

[a]Data reported by Pagani et al. (2022); all participants without prior (SOFT) or without concurrent chemotherapy (TEXT)

[b]Data reported by Gnant et al. (2015); prior chemotherapy was allowed

[c]Data reported by Pagani et al. (2022); all participants with prior (SOFT) or with concurrent chemotherapy (TEXT)

Figure 84 Overall survival – 8 to 12 years follow-up – subgroup analysis by use of chemotherapy – RE model (I2 >50%)

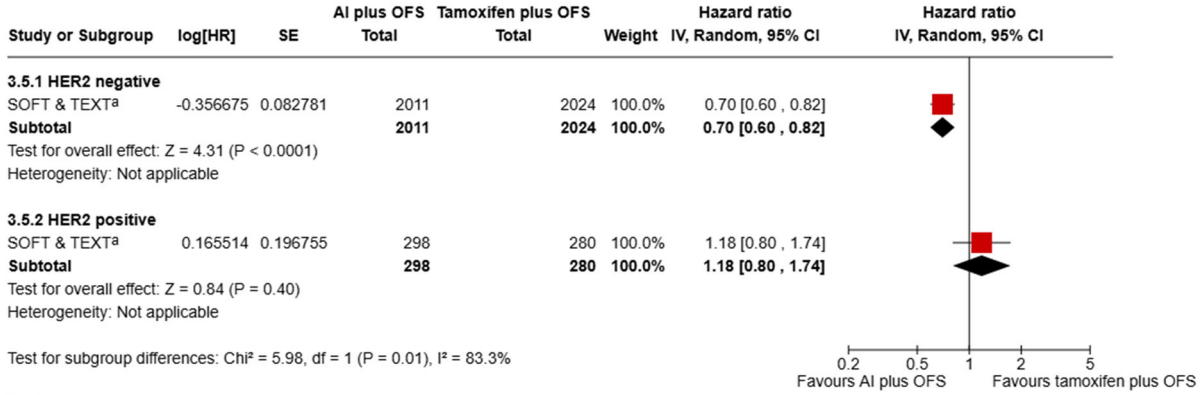


Footnotes

[a]Data reported by Gnant et al. (2015); prior chemotherapy was allowed

[b]Data reported by Pagani et al. (2022); all participants with prior (SOFT) or with concurrent chemotherapy (TEXT)

Figure 85 Overall survival – 8 years follow-up – subgroup analysis by HER2 status

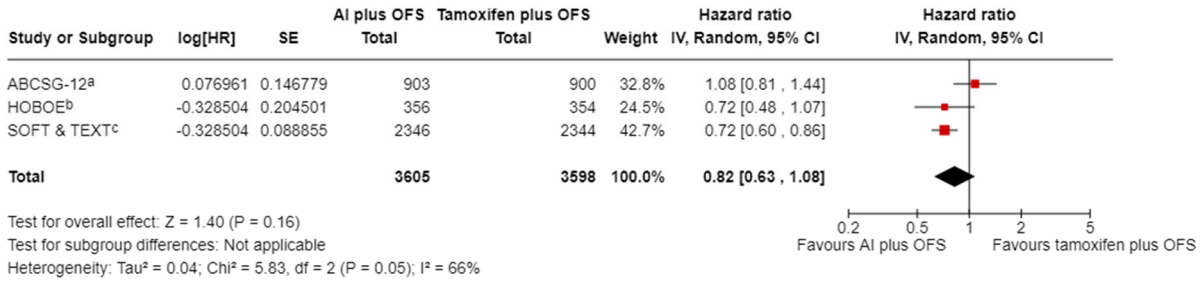


Footnotes

[a]Data reported by Francis et al. (2018)

Disease-free survival

Figure 86 Disease-free survival – 5 years follow-up (all with method of OFS: luteinising-hormone releasing hormone agonists)



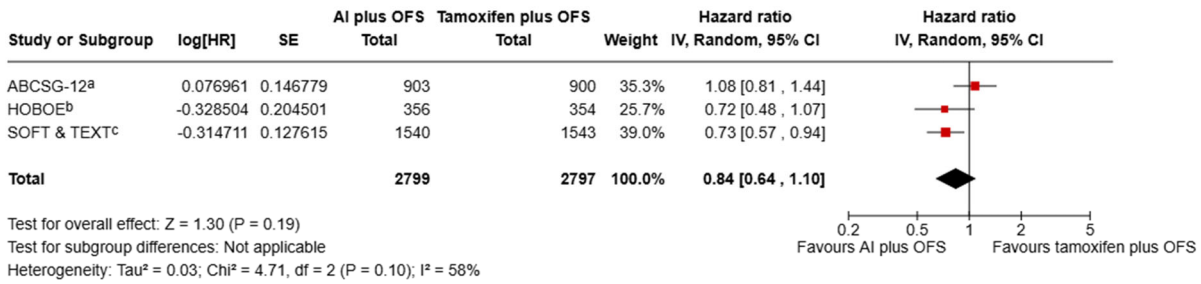
Footnotes

[a]Data reported by Gnant et al. (2011)

[b]Data reported by Perrone et al. (2019)

[c]Data reported by Pagani et al. (2014)

Figure 87 Disease-free survival – 5 years follow-up sensitivity analysis without study with concurrent chemotherapy (TEXT study)

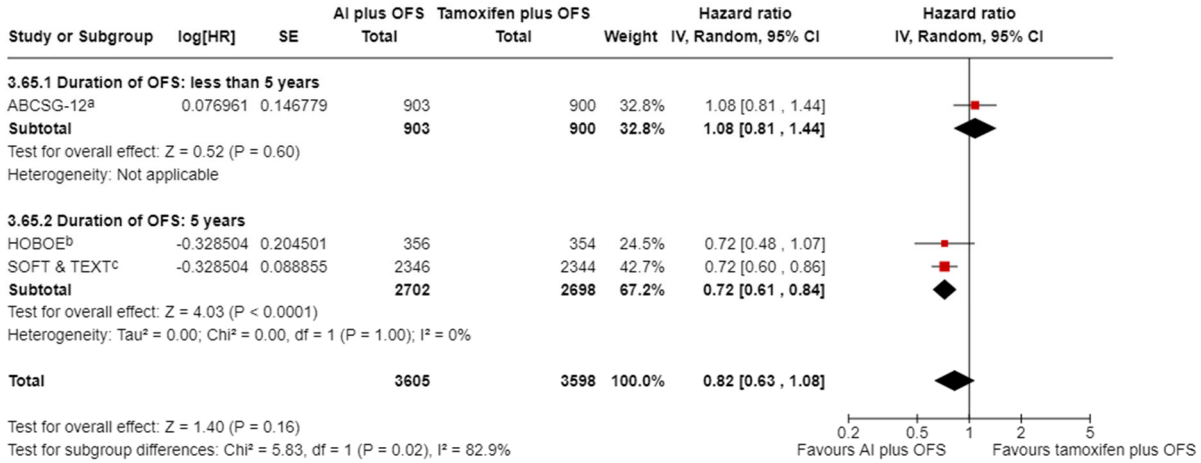


Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.03; Chi² = 4.71, df = 2 (P = 0.10); I² = 58%

Footnotes

[a]Data reported by Gnant et al. (2011); prior chemotherapy was allowed
[b]Data reported by Perrone et al. (2019); prior chemotherapy was allowed
[c]Data reported by Pagani et al. (2014); prior chemotherapy was allowed (SOFT) or without concurrent chemotherapy (TEXT)

Figure 88 Disease-free survival – 5 years follow-up – subgroup analysis by duration of OFS (RE model to match main analysis)



Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Chi² = 5.83, df = 1 (P = 0.02), I² = 82.9%
Heterogeneity: Tau² = 0.04; Chi² = 5.83, df = 2 (P = 0.05); I² = 66%

Footnotes

[a]Data reported by Gnant et al. (2011); goserelin for 3 years
[b]Data reported by Perrone et al. (2019); triptorelin for 5 years
[c]Data reported by Pagani et al. (2014); triptorelin for 5 years

Figure 89 Disease-free survival – 5 years follow-up – subgroup analysis by age

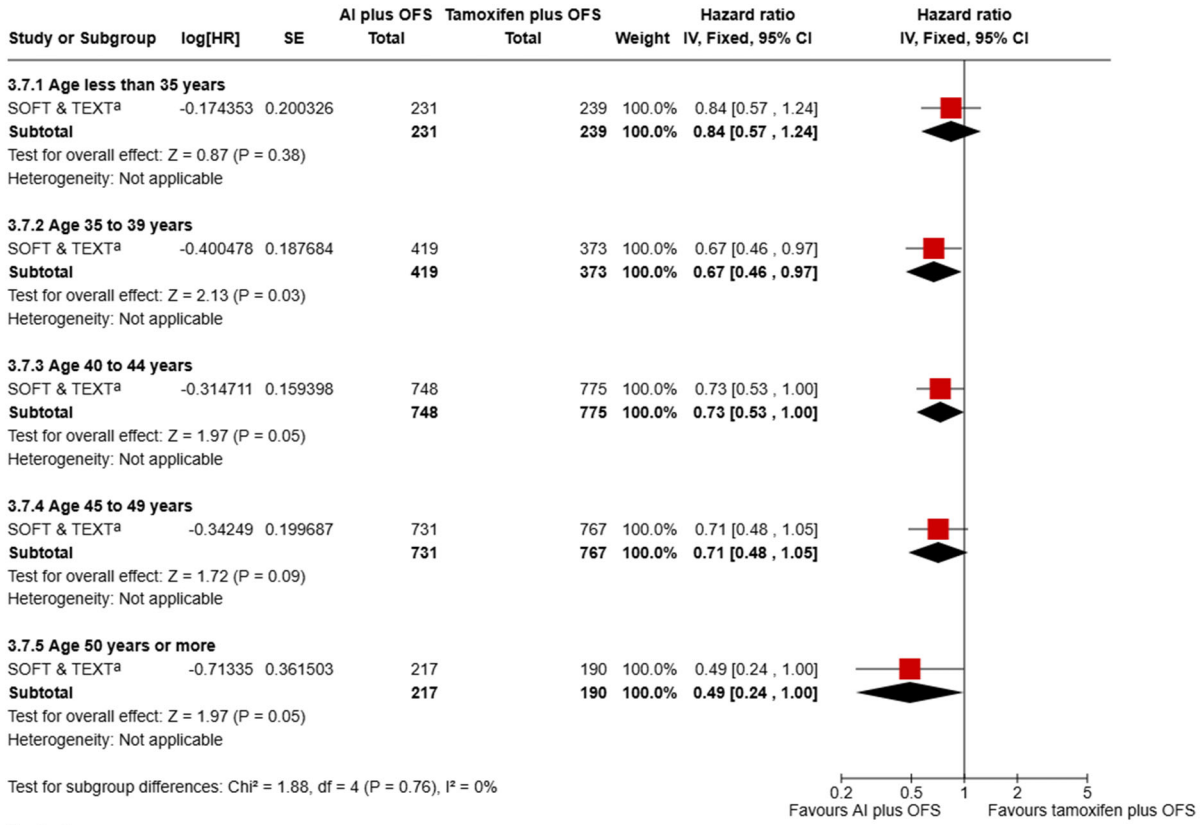


Figure 90 Disease-free survival – 5 years follow-up – subgroup analysis by lymph node status

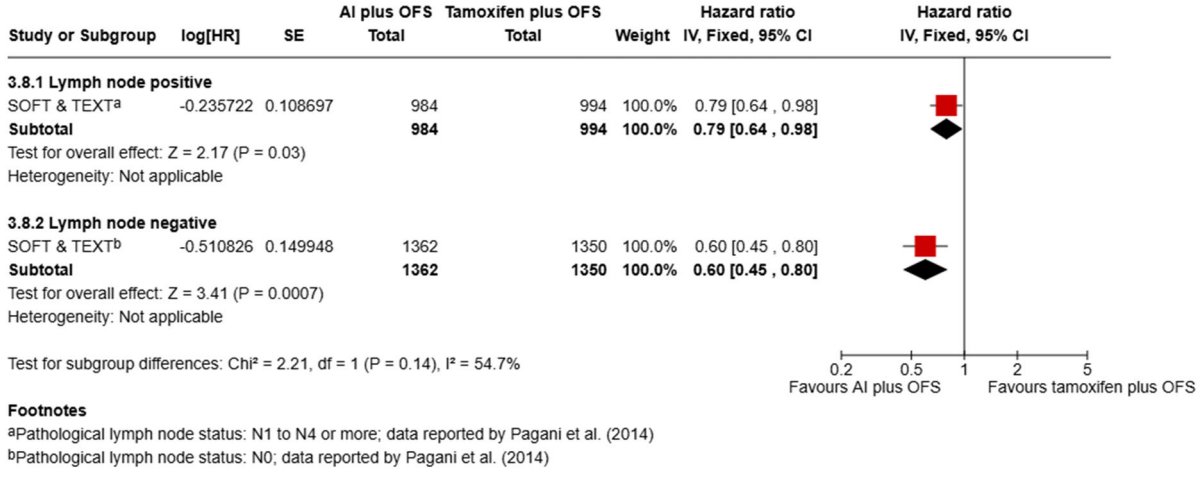
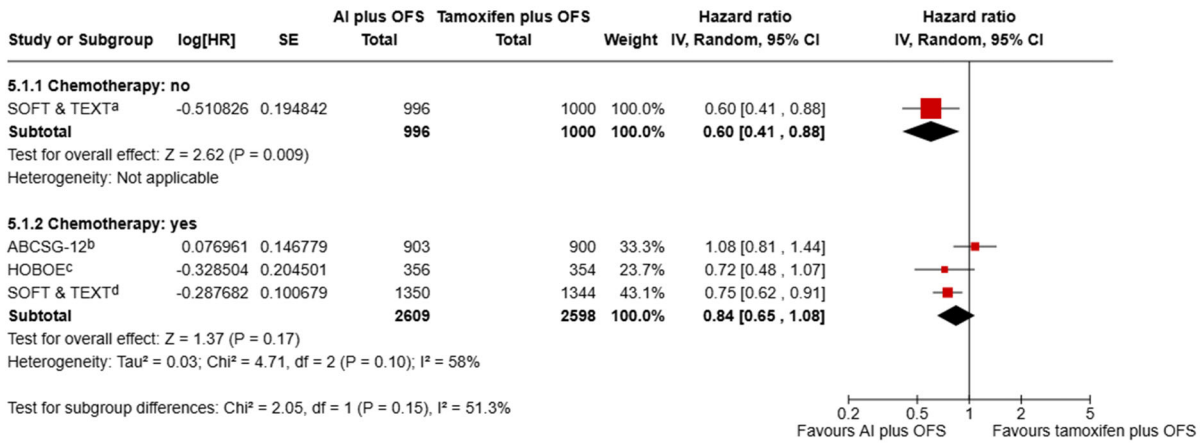


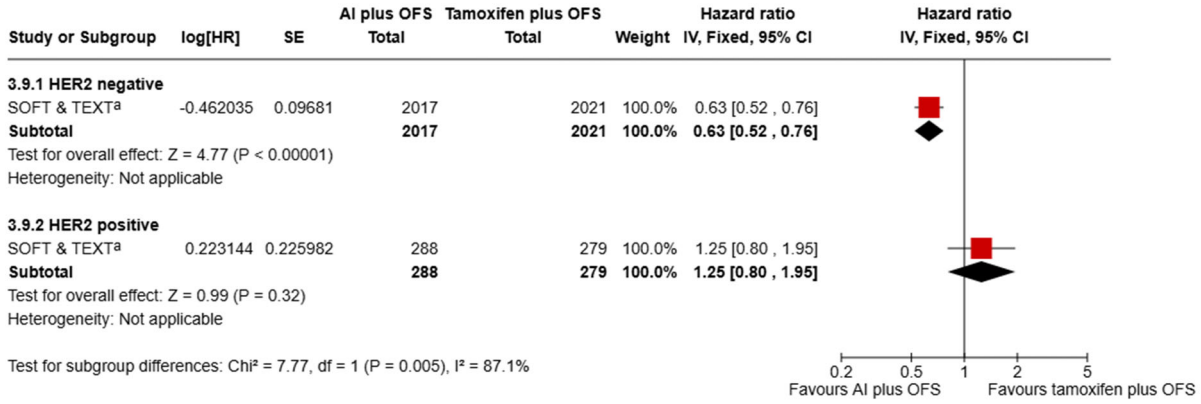
Figure 91 Disease-free survival – 5 years follow-up – subgroup analysis by use of chemotherapy



Footnotes

[a]Data reported by Pagani et al. (2014); all participants without prior chemotherapy (SOFT) or without concurrent chemotherapy (TEXT)
[b]Data reported by Gnant et al. (2011); prior chemotherapy was allowed
[c]Data reported by Perrone et al. (2019); prior chemotherapy was allowed
[d]Data reported by Pagani et al. (2014); all participants with prior chemotherapy (SOFT) or with concurrent chemotherapy (TEXT)

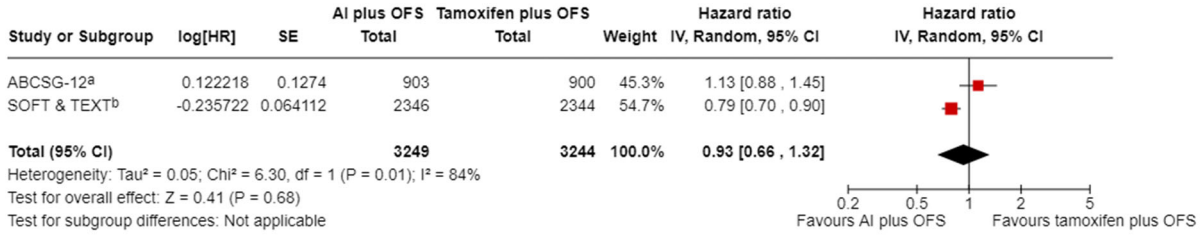
Figure 92 Disease-free survival – 5 years follow-up – subgroup analysis by HER2 status



Footnotes

[a]Data reported by Pagani et al. (2014)

Figure 93 Disease-free survival – 8 to 12 years follow-up (all with method of OFS: luteinising-hormone releasing hormone agonists)

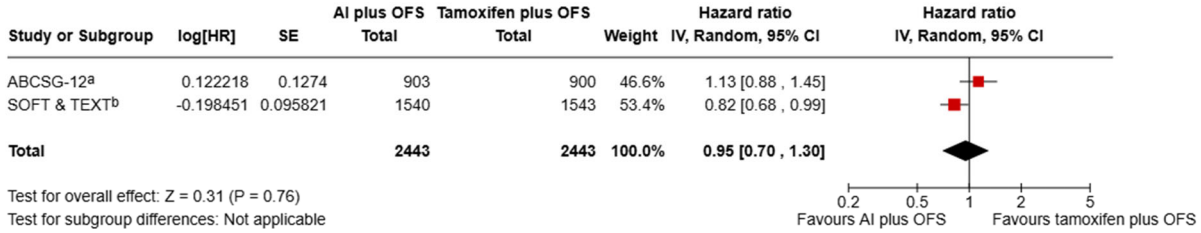


Footnotes

[a]Follow-up: 8 years; data reported by Gnant et al. (2015)

[b]Follow-up: 12 years; data reported by Pagani et al. (2022)

Figure 94 Disease-free survival – 8 years follow-up sensitivity analysis without study with concurrent chemotherapy (TEXT study)

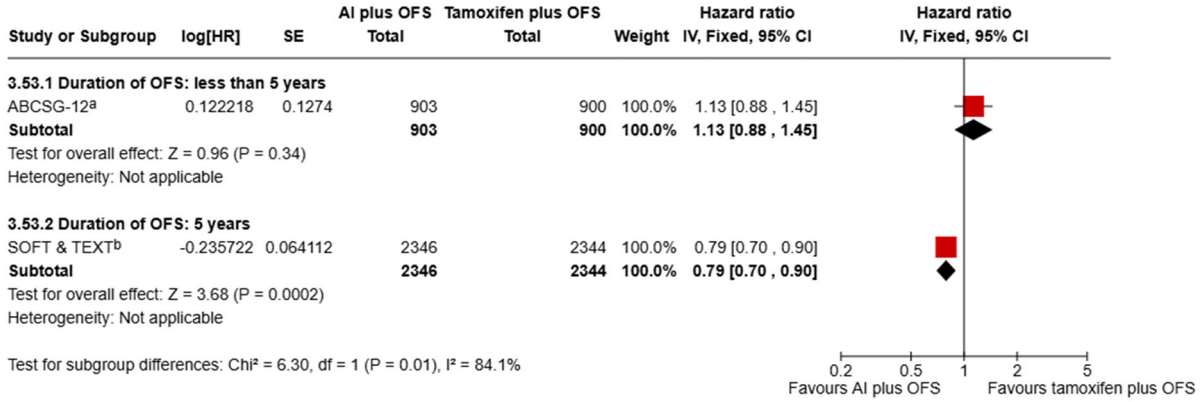


Footnotes

[a]Follow-up: 8 years; data reported by Gnant et al. (2015); prior chemotherapy was allowed

[b]Follow-up: 8 years; data reported by Francis et al. (2018); prior chemotherapy allowed (SOFT) or without concurrent chemotherapy (TEXT)

Figure 95 Disease-free survival – 8 to 12 years follow-up – subgroup analysis by duration of OFS

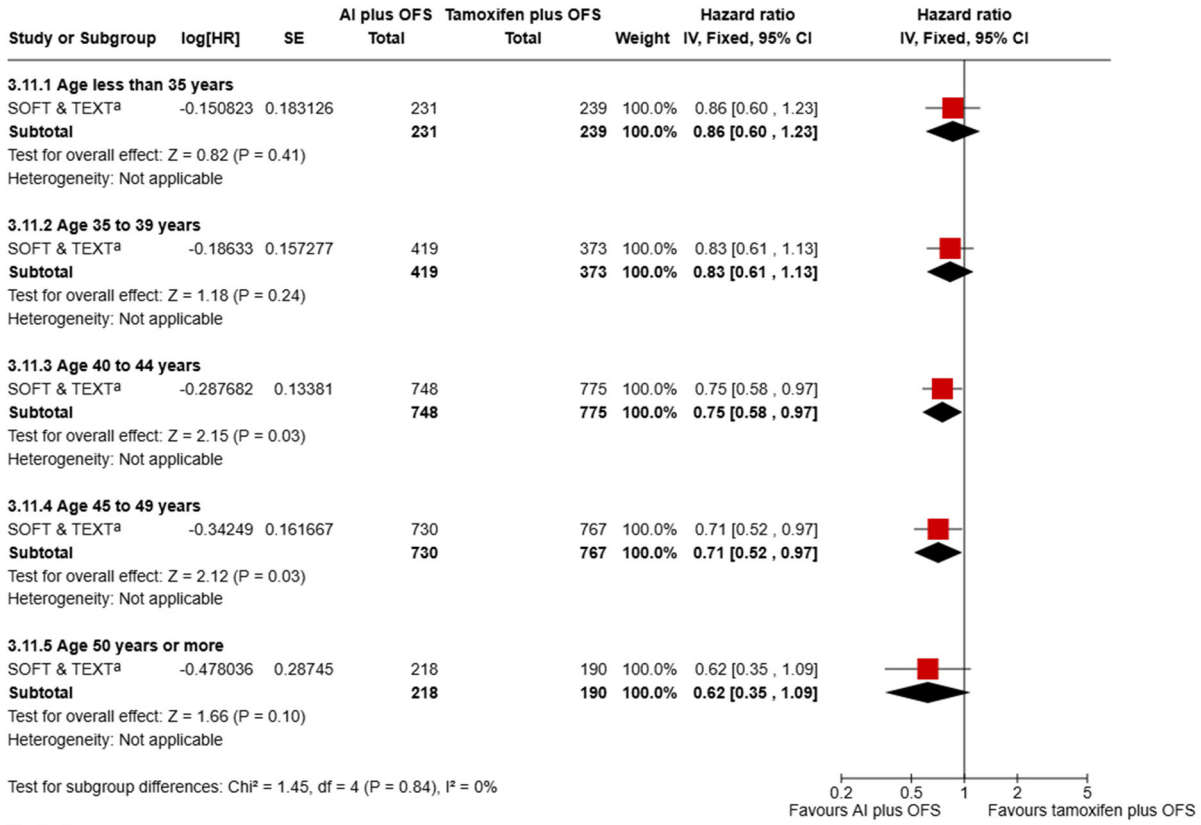


Footnotes

[a]Follow-up: 8 years; data reported by Gnant et al. (2015)

[b]Follow-up: 12 years; data reported by Pagani et al. (2022); triptorelin for 5 years

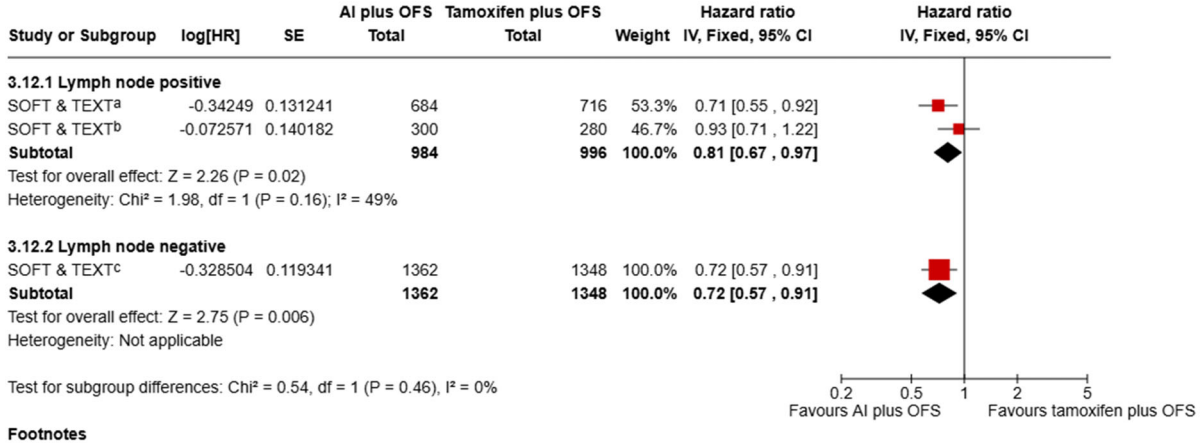
Figure 96 Disease-free survival – 8 years follow-up – subgroup analysis by age



Footnotes

[a]Data reported by Francis et al. (2018)

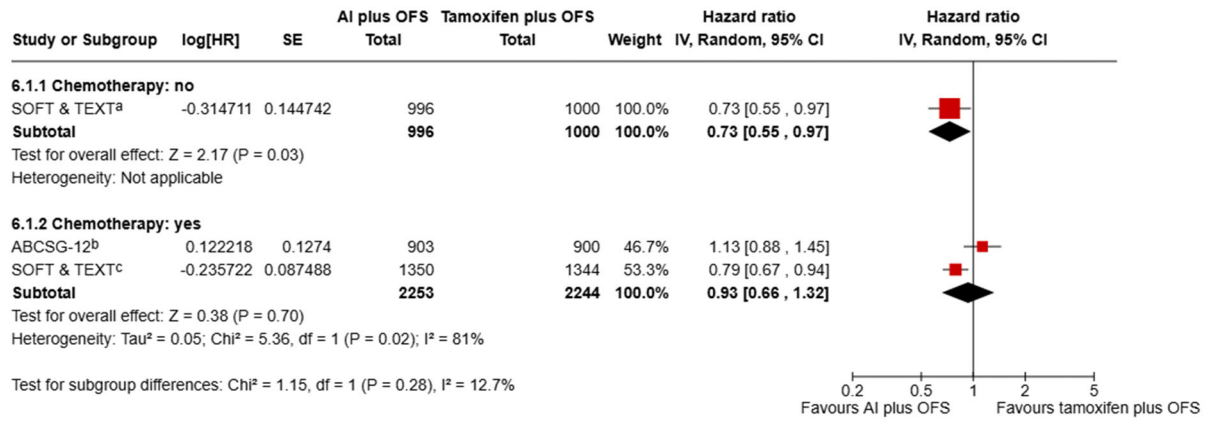
Figure 97 Disease-free survival – 8 years follow-up – subgroup analysis by lymph node status



Footnotes

[a]Pathological lymph node status: N1 to N3; data reported by Francis et al. (2018)
[b]Pathological lymph node status: N4 or more; data reported by Francis et al. (2018)
[c]Pathological lymph node status: N0; data reported by Francis et al. (2018)

Figure 98 Disease-free survival – 8 years follow-up – subgroup analysis by use of chemotherapy



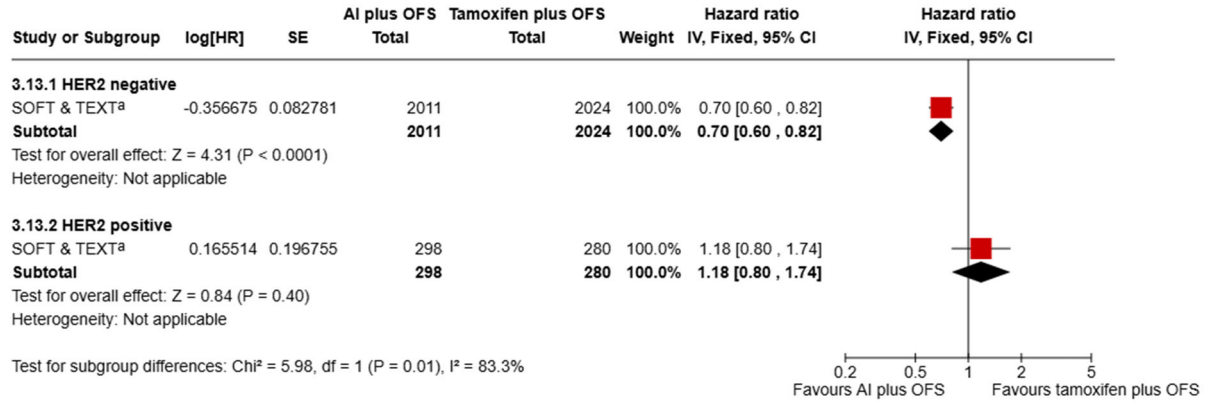
Footnotes

[a]Data reported by Francis et al. (2018); all participants without prior chemotherapy (SOFT) or without concurrent chemotherapy (TEXT)

[b]Data reported by Gnant et al. (2015); prior chemotherapy was allowed

[c]Data reported by Francis et al. (2018); all participants with prior chemotherapy (SOFT) or with concurrent chemotherapy (TEXT)

Figure 99 Disease-free survival – 8 years follow-up – subgroup analysis by HER2 status

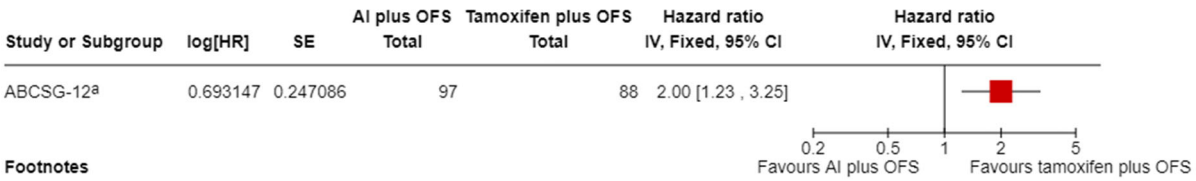


Footnotes

[a]Data reported by Francis et al. (2018)

Breast cancer mortality

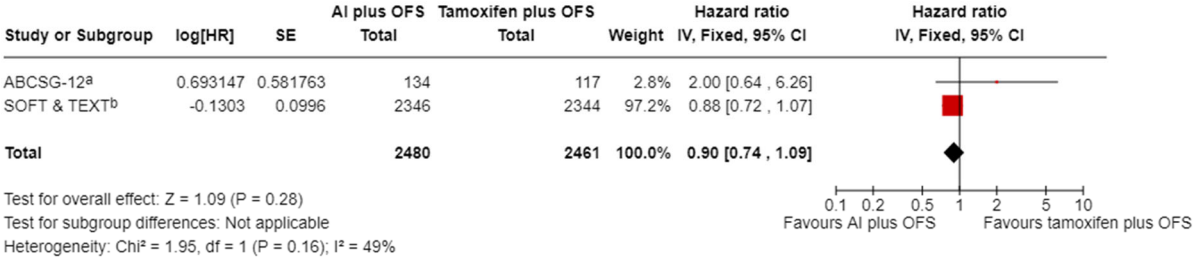
Figure 100 Breast cancer mortality – 5 years follow-up



Footnotes

[a]Totals are participants with disease recurrence; data reported by Gnant et al. (2011)

Figure 101 Breast cancer mortality – 8 to 12 years follow-up



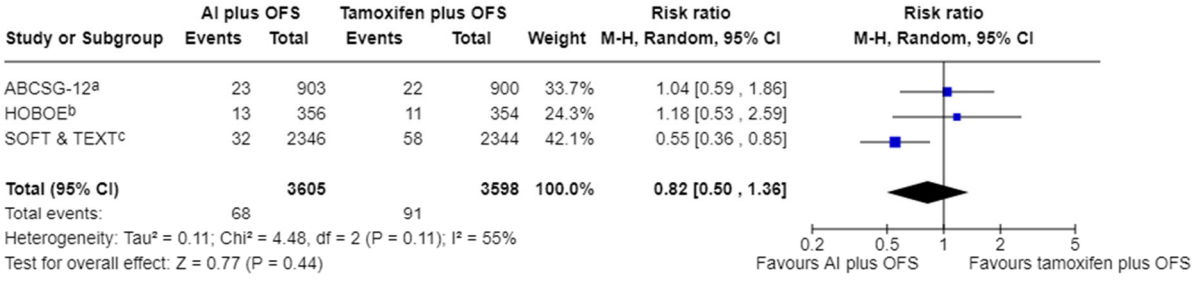
Footnotes

[a]Follow-up: 8 years; totals are participants with disease recurrence; data reported by Gnant et al. (2015)

[b]Follow-up: 12 years; log HR and SE of HR were calculated using number of events and total sample; data reported by Pagani et al. (2022)

Local and/or locoregional recurrence

Figure 102 Local and/or locoregional recurrence – 5 years follow-up



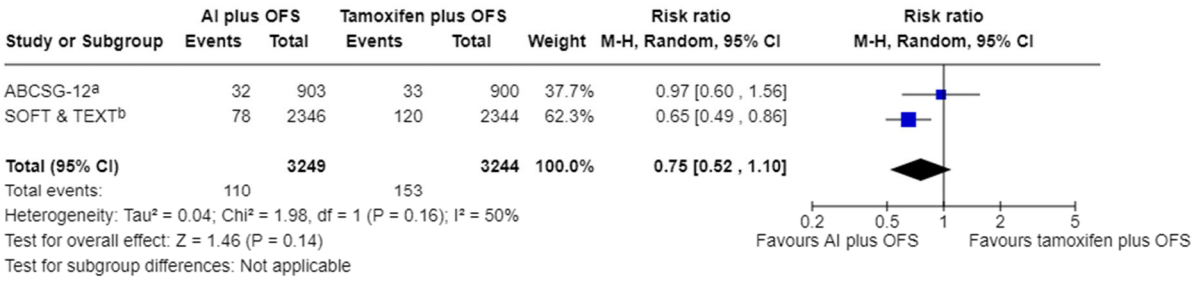
Footnotes

[a]Data reported by Gnant et al. (2011)

[b]Data reported by Perrone et al. (2019)

[c]Data reported by Pagani et al. (2014)

Figure 103 Local and /or locoregional recurrence – 8 to 12 years follow-up



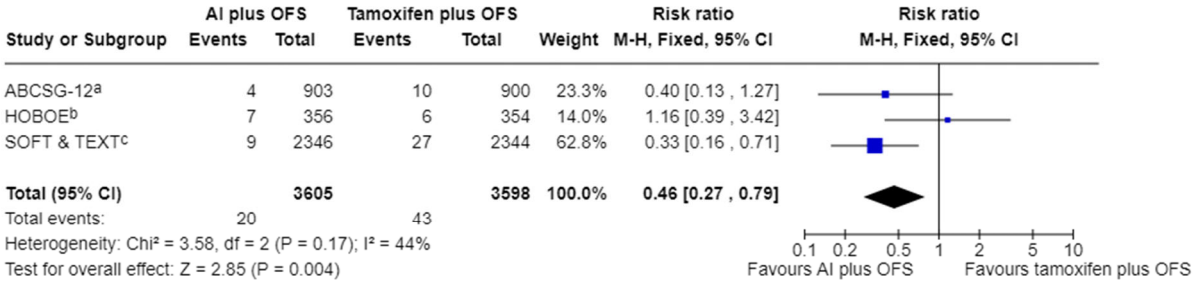
Footnotes

[a]Follow-up: 8 years; data reported by Gnant et al. (2015)

[b]Follow-up: 12 years; data reported by Pagani et al. (2022)

New contralateral disease

Figure 104 New contralateral disease – 5 years follow-up



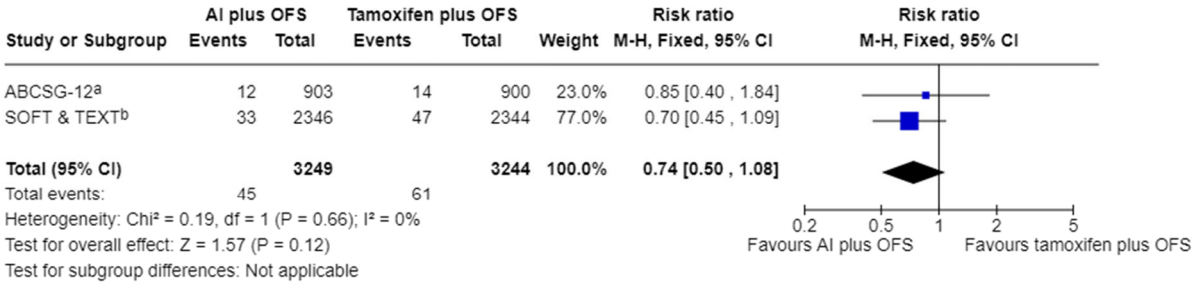
Footnotes

[a]Data reported by Gnant et al. (2011)

[b]Data reported by Perrone et al. (2019)

[c]Data reported by Pagani et al. (2014)

Figure 105 New contralateral disease – 8 to 12 years follow-up



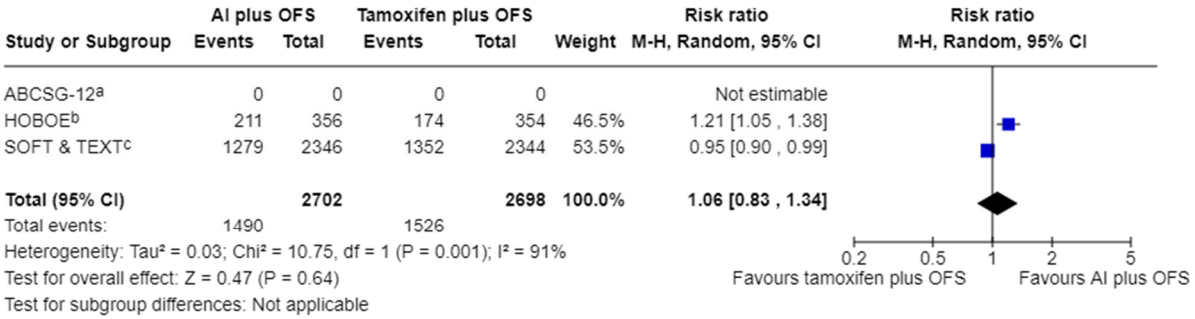
Footnotes

[a]Follow-up: 8 years; data reported by Gnant et al. (2015)

[b]Follow-up: 12 years; data reported by Pagani et al. (2022)

Adherence to or completion of treatment

Figure 106 Adherence to or completion of treatment (treatment completed at 5 years)



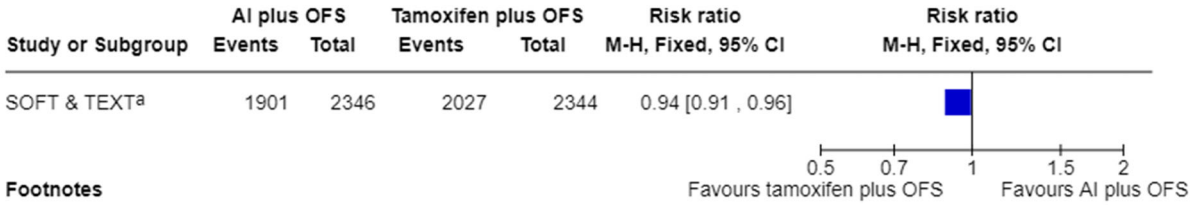
Footnotes

[a]Data reported by Gnant et al. (2011)

[b]Data reported by Perrone et al. (2019)

[c]Data reported by Pagani et al. (2014); number of events calculated from percentages

Figure 107 Adherence to or completion of treatment (treatment completed at 8 years)



Footnotes

[a]Data reported by Francis et al. (2018)

Quality of life

No evidence for this outcome.

Adverse events

Figure 108 Adverse events – genitourinary: vaginal dryness – 5 years follow-up

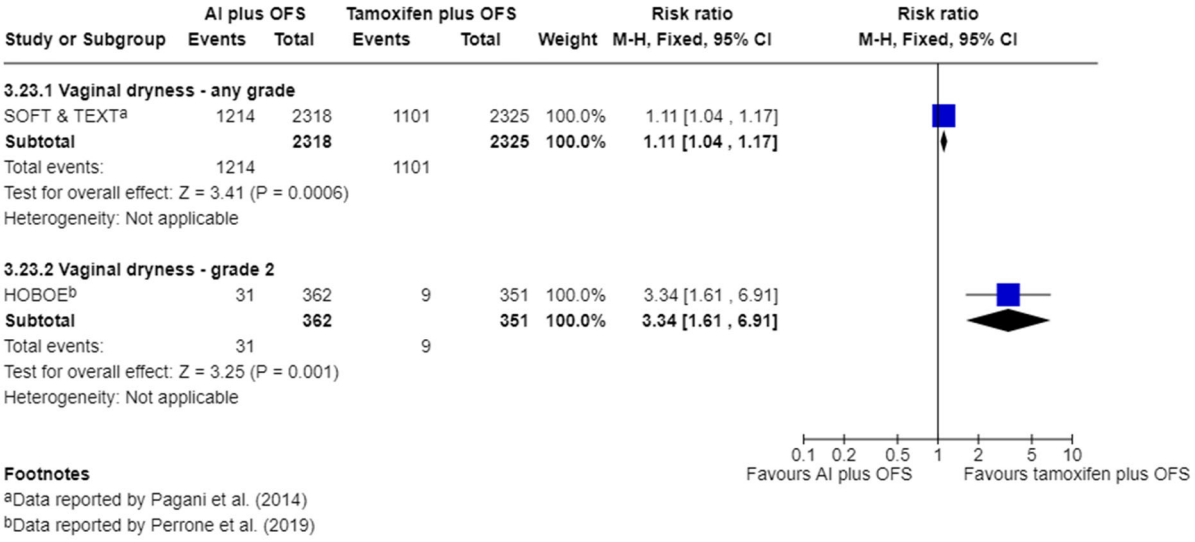


Figure 109 Adverse events – genitourinary: vaginal dryness (any grade) – 8 years follow-up

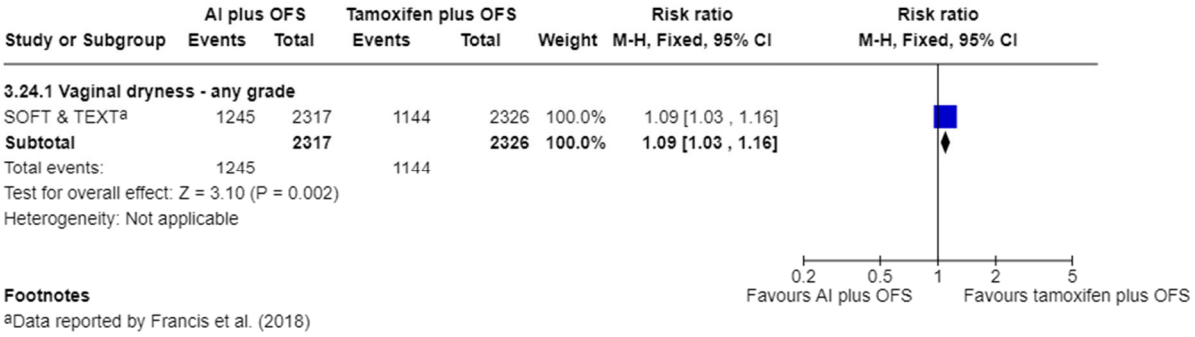


Figure 110 Adverse events – genitourinary: incontinence – 5 years follow-up

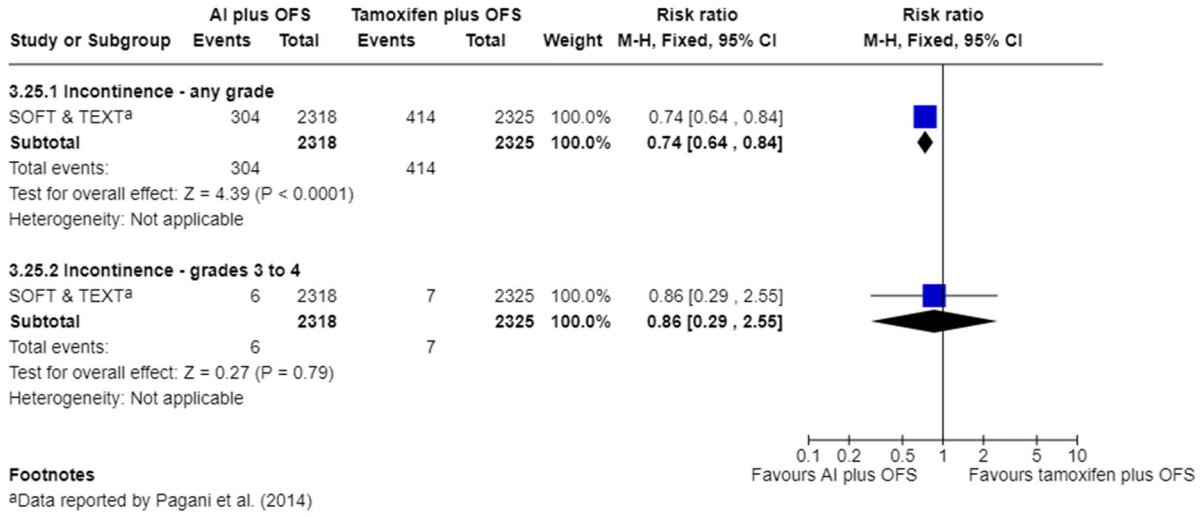


Figure 111 Adverse events – genitourinary: incontinence – 8 years follow-up

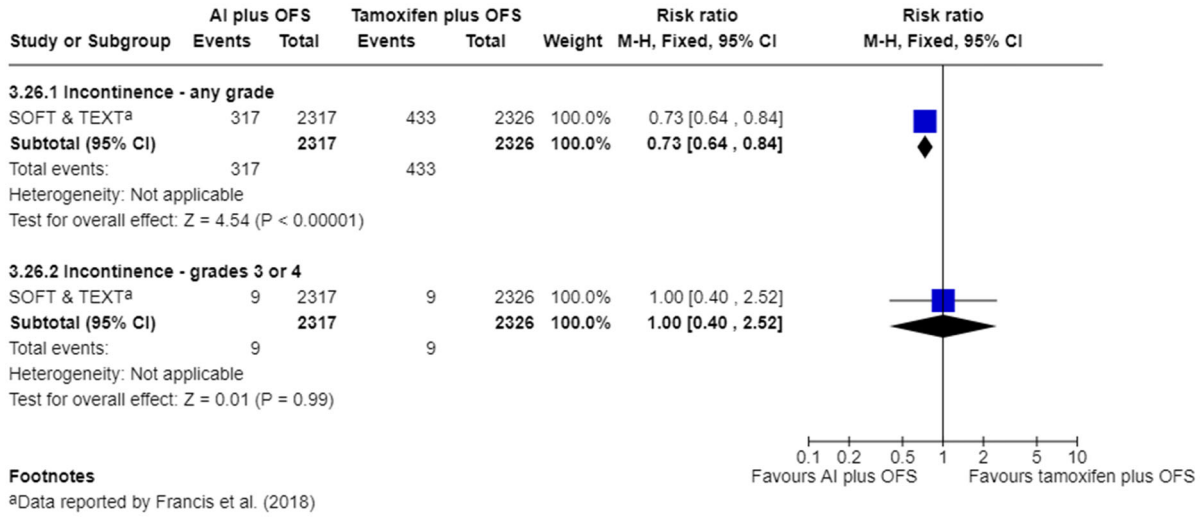
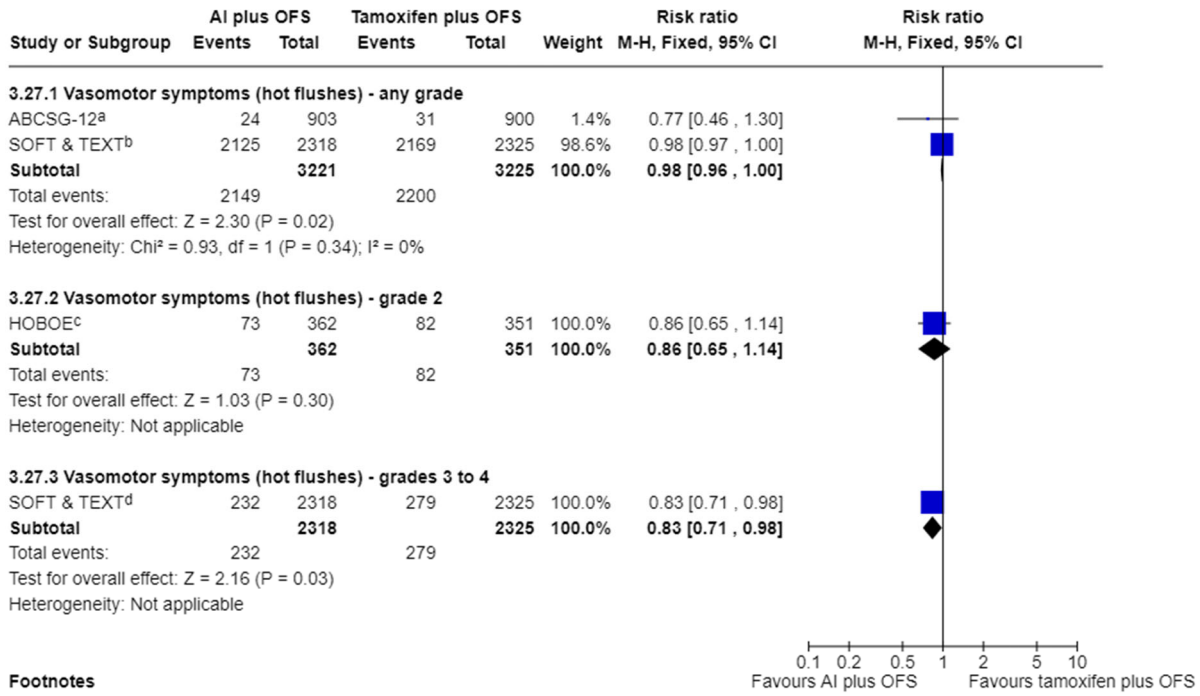


Figure 112 Adverse events – menopausal symptoms: vasomotor – 5 years follow-up



Footnotes

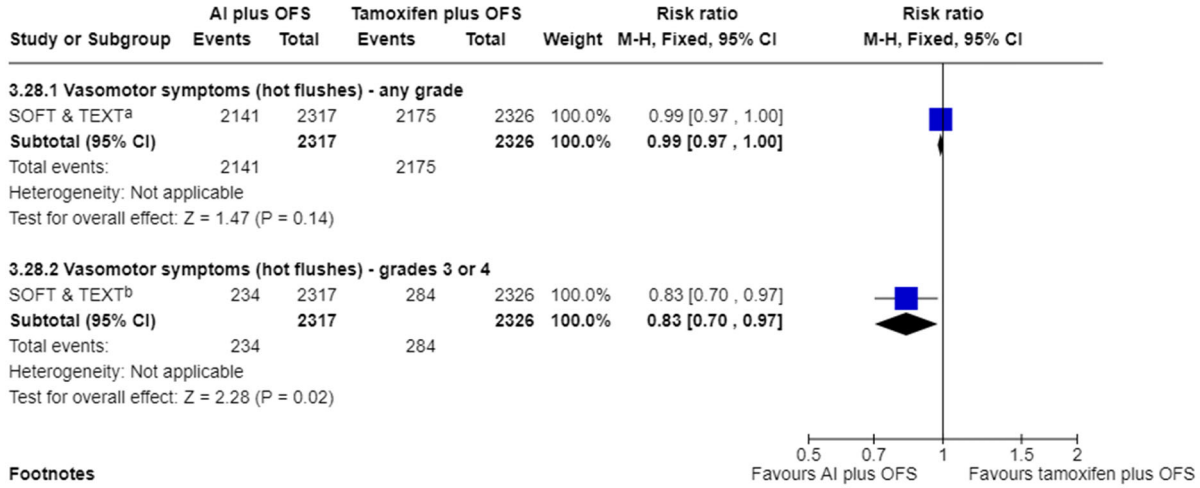
[a]Data reported by Gnant et al. (2011); grade of adverse event was not reported

[b]Data reported by Pagani et al. (2014); adverse event reported as any grade. Only data for hot flushes reported to avoid double counting

[c]Data reported by Perrone et al. (2019)

[d]Data reported by Pagani et al. (2014)

Figure 113 Adverse events – menopausal symptoms: vasomotor – 8 years follow-up

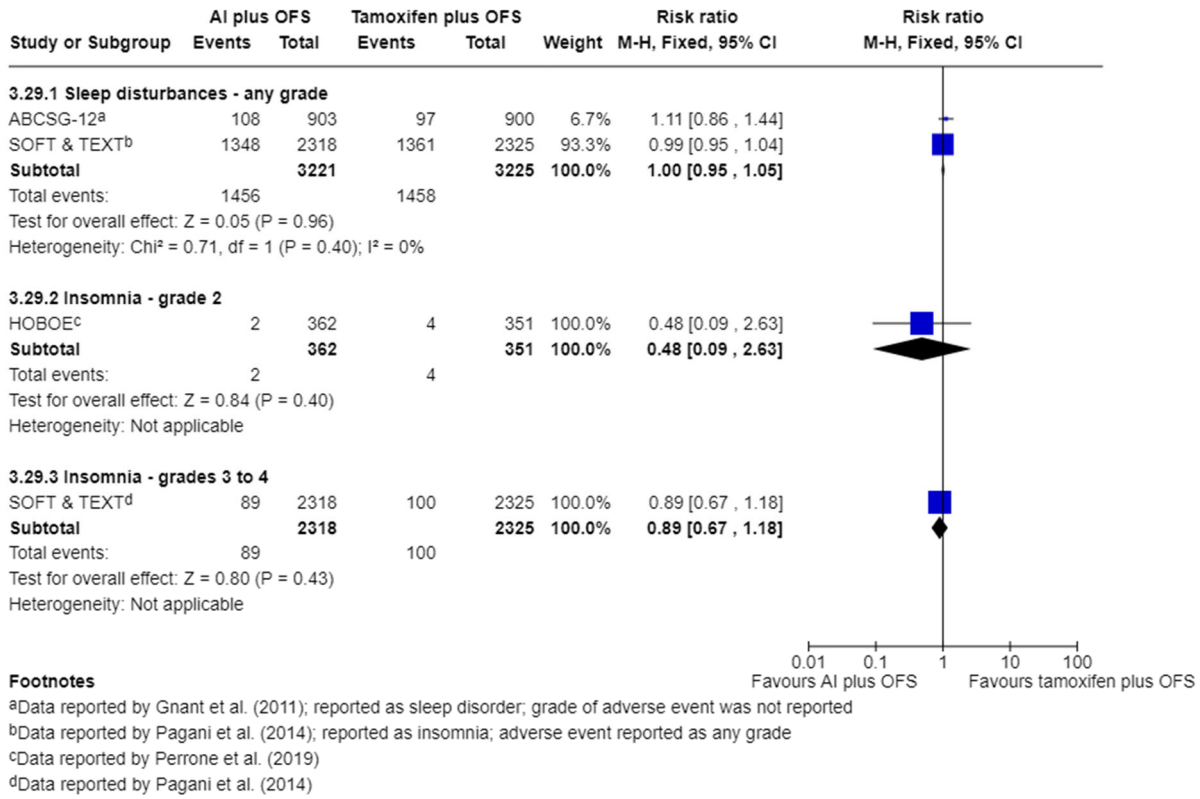


Footnotes

[a]Data reported by Francis et al. (2018). Only data for hot flushes reported to avoid double counting

[b]Data reported by Francis et al. (2018)

Figure 114 Adverse events – menopausal symptoms: sleep disturbance – 5 years follow-up



Footnotes

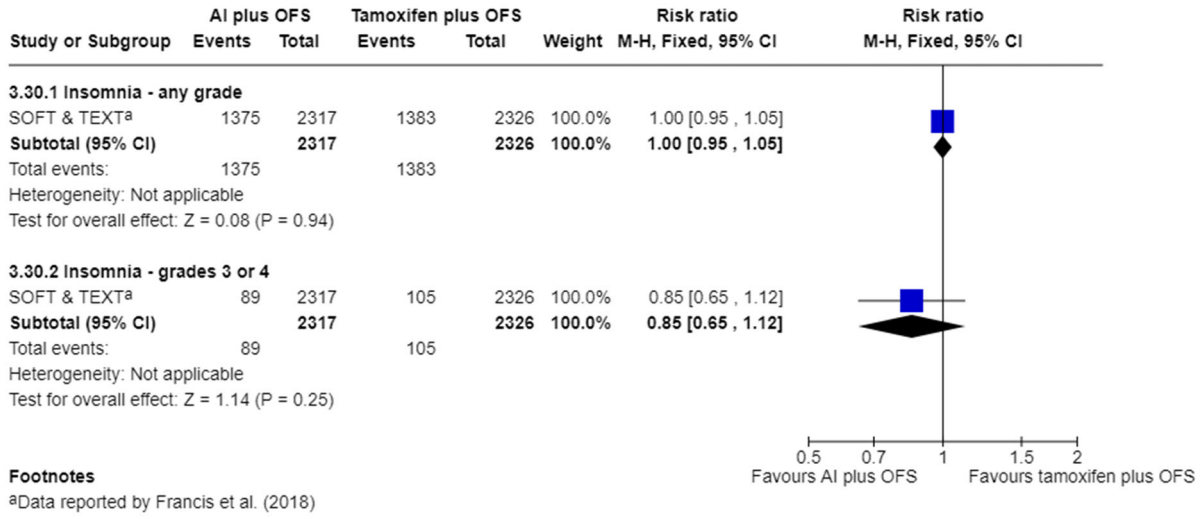
[a]Data reported by Gnant et al. (2011); reported as sleep disorder; grade of adverse event was not reported

[b]Data reported by Pagani et al. (2014); reported as insomnia; adverse event reported as any grade

[c]Data reported by Perrone et al. (2019)

[d]Data reported by Pagani et al. (2014)

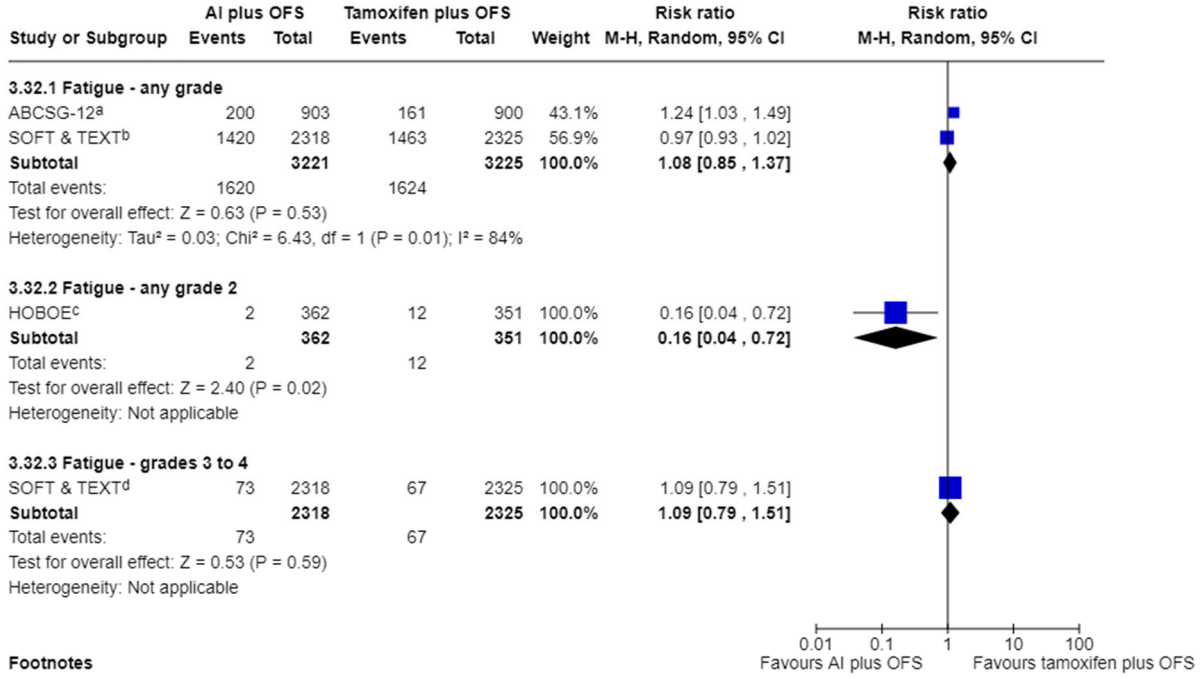
Figure 115 Adverse events – menopausal symptoms: sleep disturbances – 8 years follow-up



Footnotes

[a]Data reported by Francis et al. (2018)

Figure 116 Adverse events – menopausal symptoms: fatigue – 5 years follow-up



Footnotes

[a]Data reported by Gnant et al. (2011); grade of adverse event was not reported
[b]Data reported by Pagani et al. (2014); adverse event reported as any grade
[c]Data reported by Perrone et al. (2019)
[d]Data reported by Pagani et al. (2014)

Figure 117 Adverse events – menopausal symptoms: fatigue – 8 years follow-up

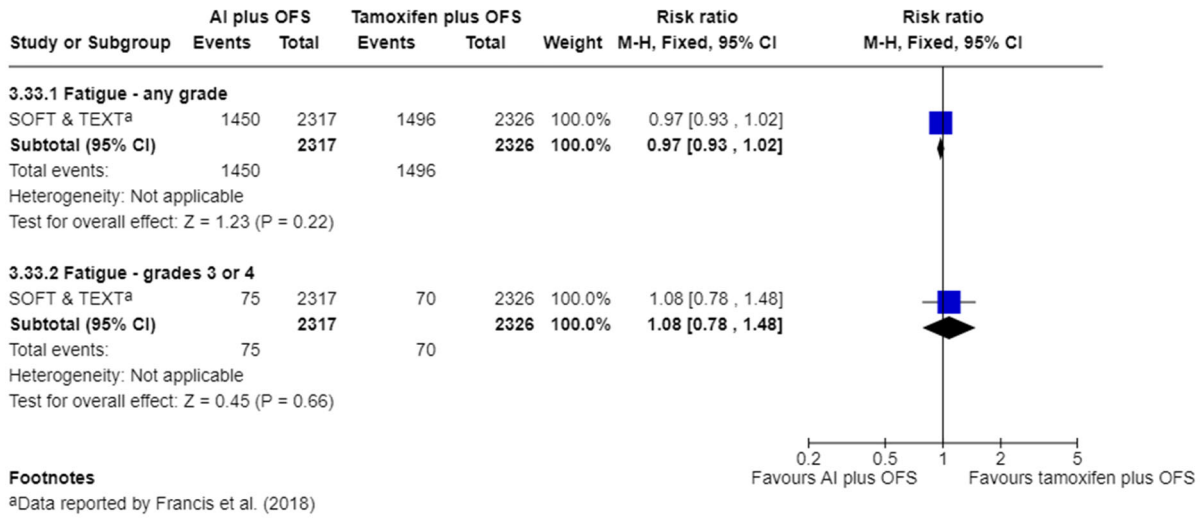


Figure 118 Adverse events – menopausal symptoms: weight gain – 5 years follow-up

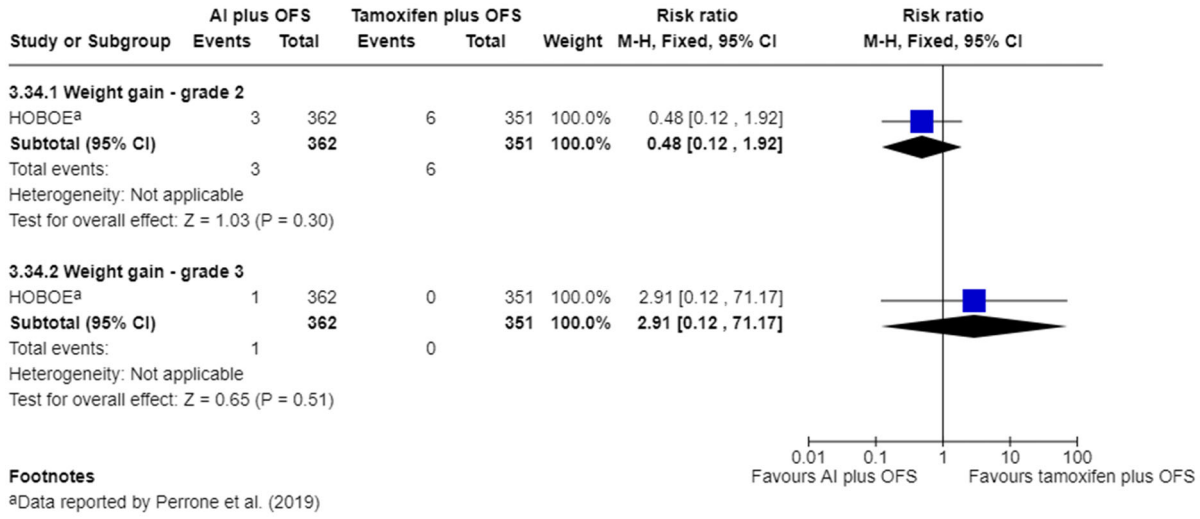


Figure 119 Adverse events – hypercholesterolaemia – 5 years follow-up (grade 2)

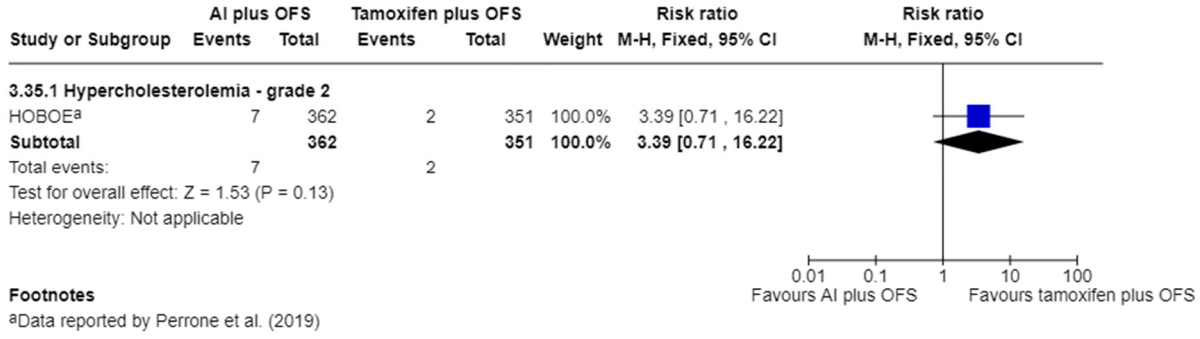
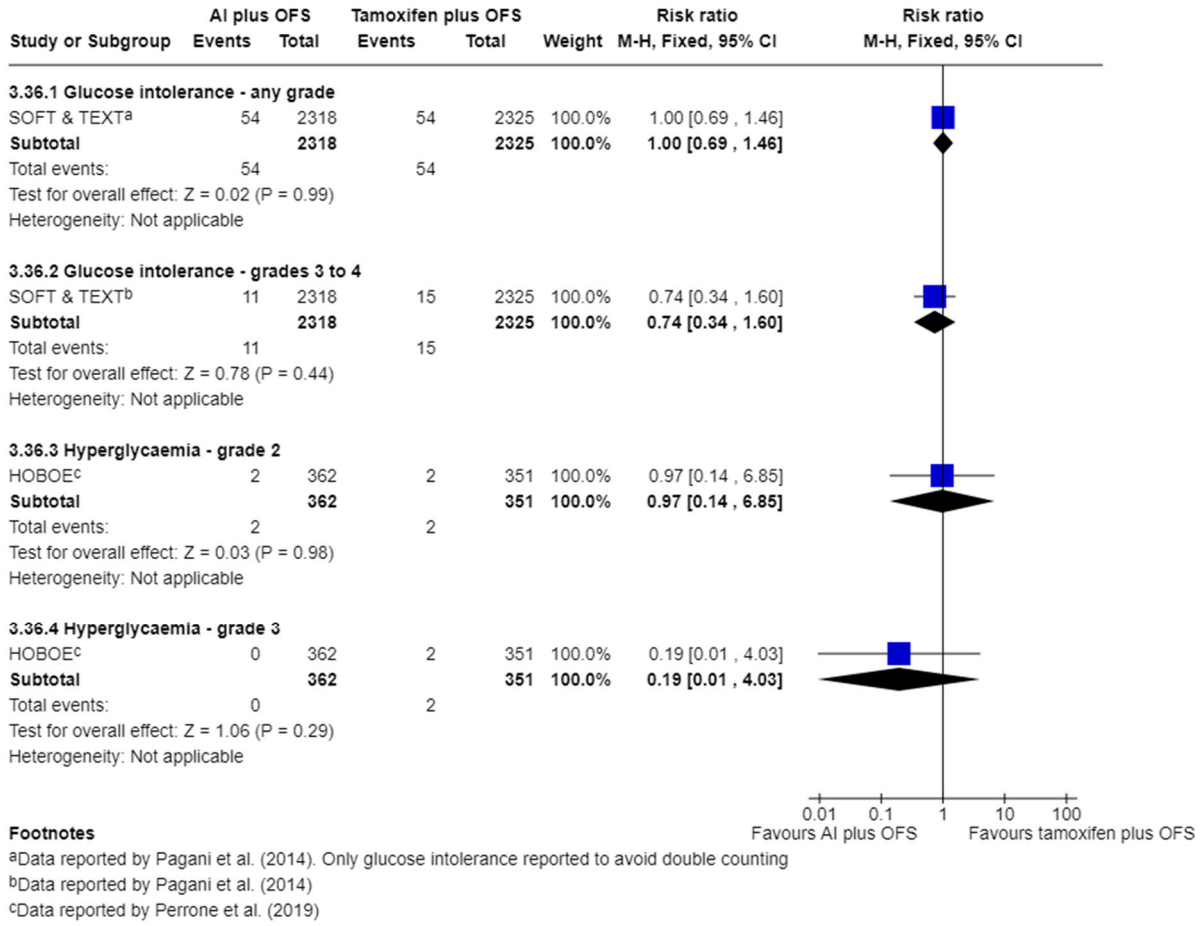


Figure 120 Adverse events – glucose intolerance and hyperglycaemia– 5 years follow-up



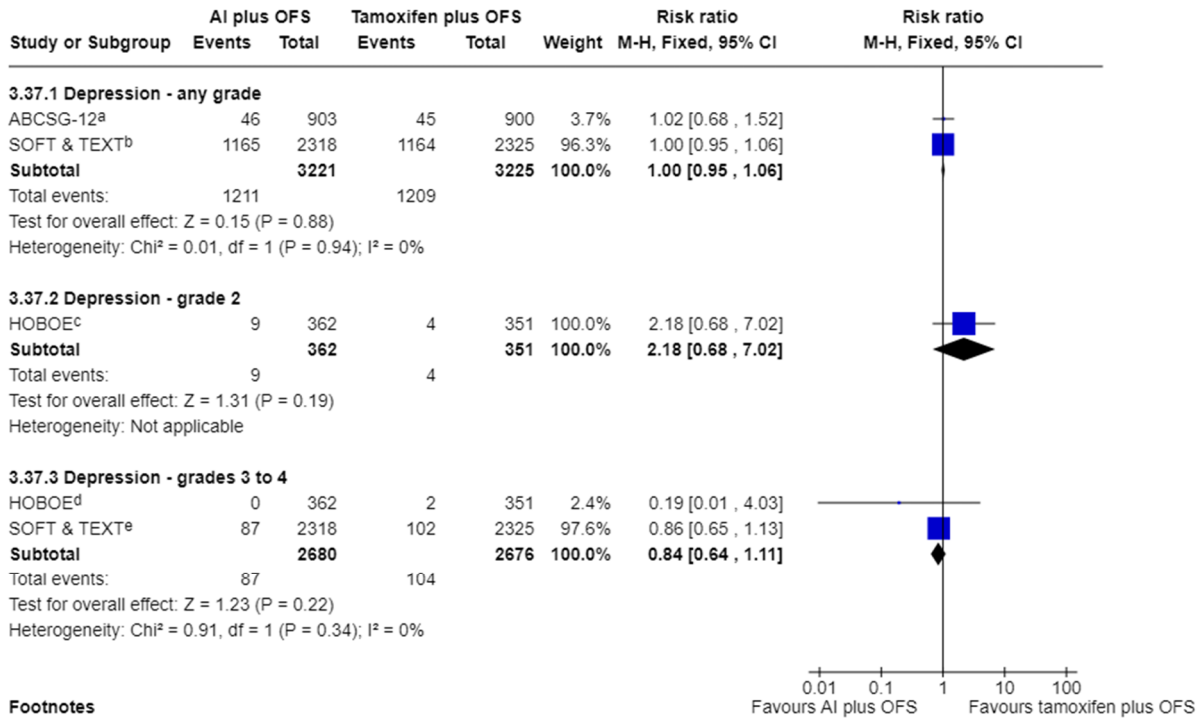
Footnotes

[a]Data reported by Pagani et al. (2014). Only glucose intolerance reported to avoid double counting

[b]Data reported by Pagani et al. (2014)

[c]Data reported by Perrone et al. (2019)

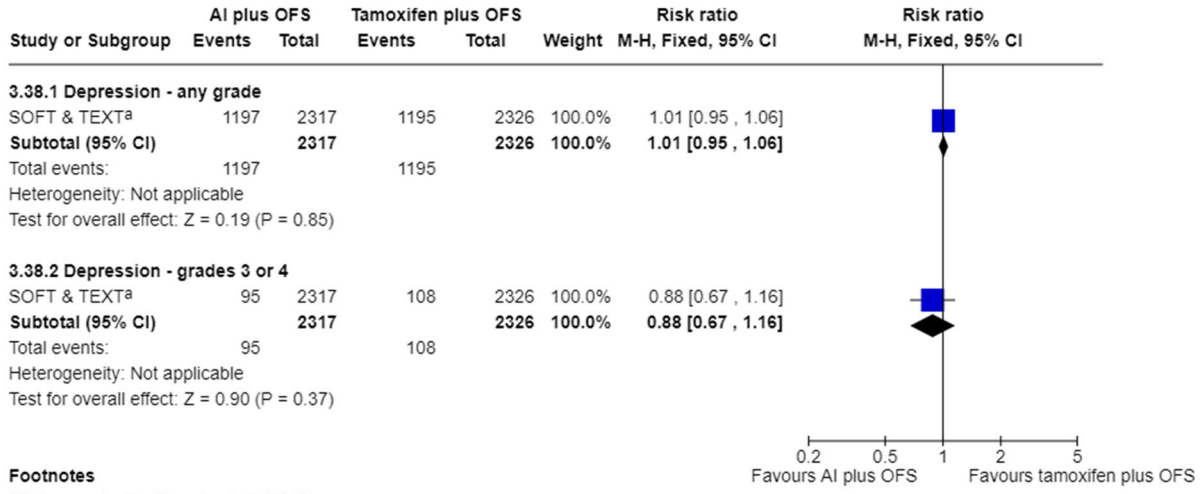
Figure 121 Adverse events – neurocognitive – 5 years follow-up: depression



Footnotes

[a]Data reported by Gnant et al. (2011); grade of adverse event was not reported
[b]Data reported by Pagani et al. (2014); adverse event reported as any grade
[c]Data reported by Perrone et al. (2019)
[d]Data reported by Perrone et al. (2019); adverse event reported as grade 3
[e]Data reported by Pagani et al. (2014); adverse event reported as grades 3 to 4

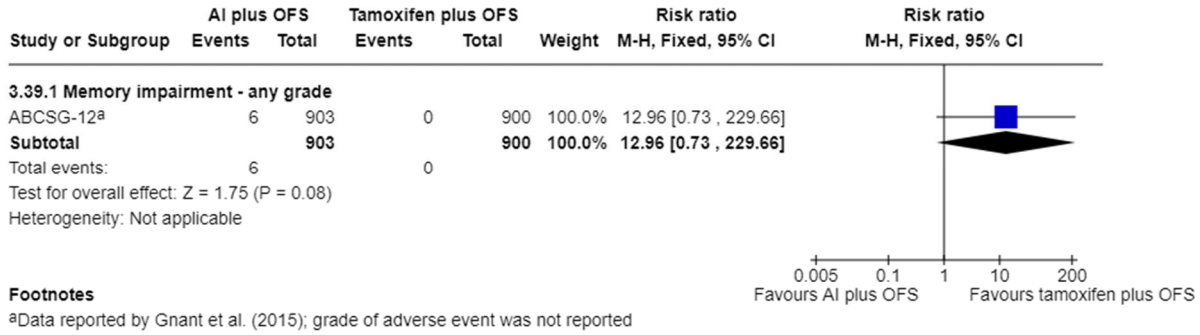
Figure 122 Adverse events – neurocognitive – 8 years follow-up: depression



Footnotes

[a]Data reported by Francis et al. (2018)

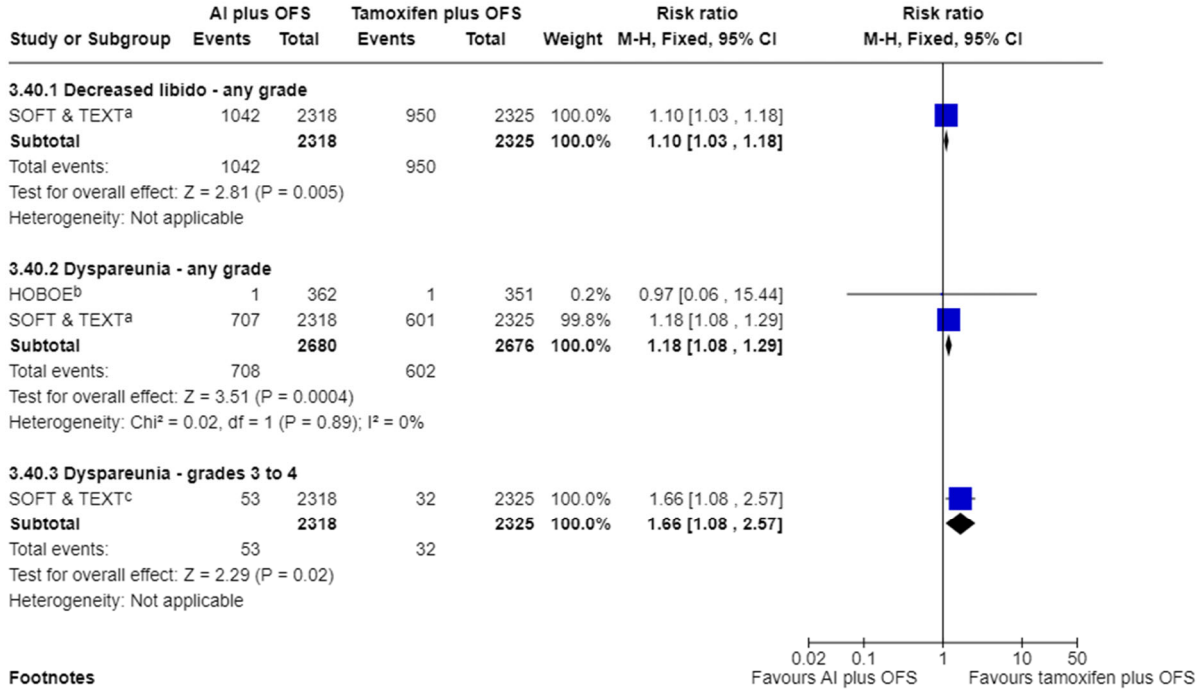
Figure 123 Adverse events – neurocognitive – 8 years follow-up: memory impairment



Footnotes

[a]Data reported by Gnant et al. (2015); grade of adverse event was not reported

Figure 124 Adverse events – psychosexual: sexual function– 5 years follow-up



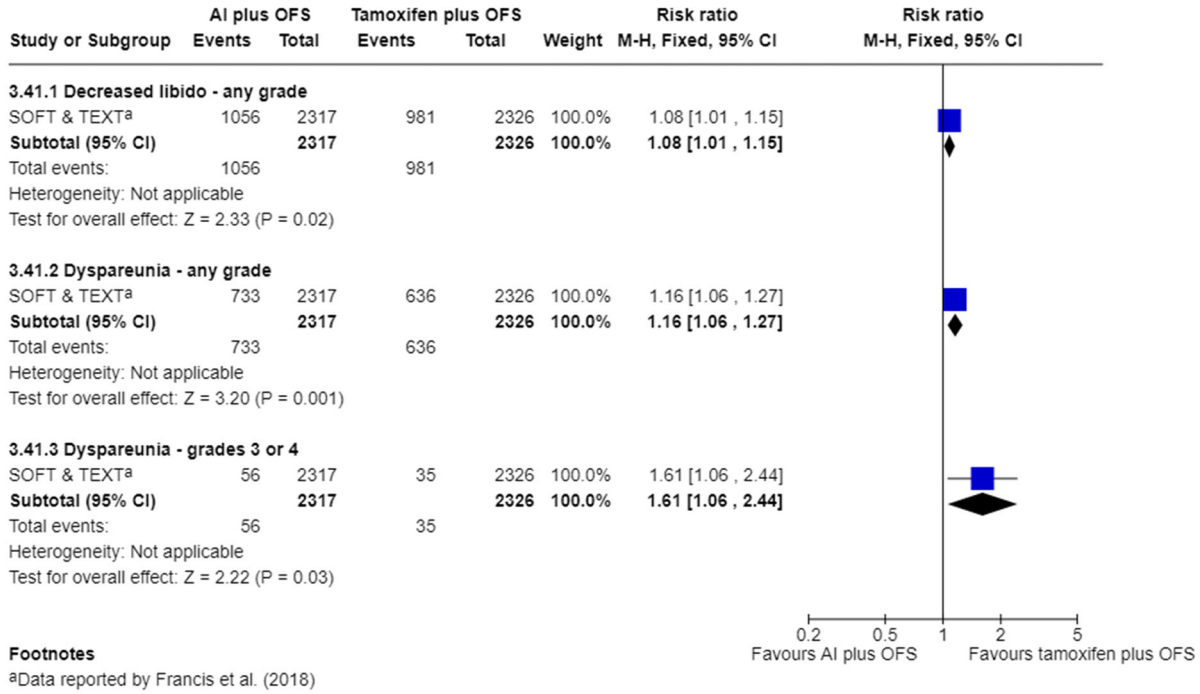
Footnotes

[a]Data reported by Pagani et al. (2014); adverse event reported as any grade

[b]Data reported by Perrone et al. (2019); adverse event reported as grade 2

[c]Data reported by Pagani et al. (2014)

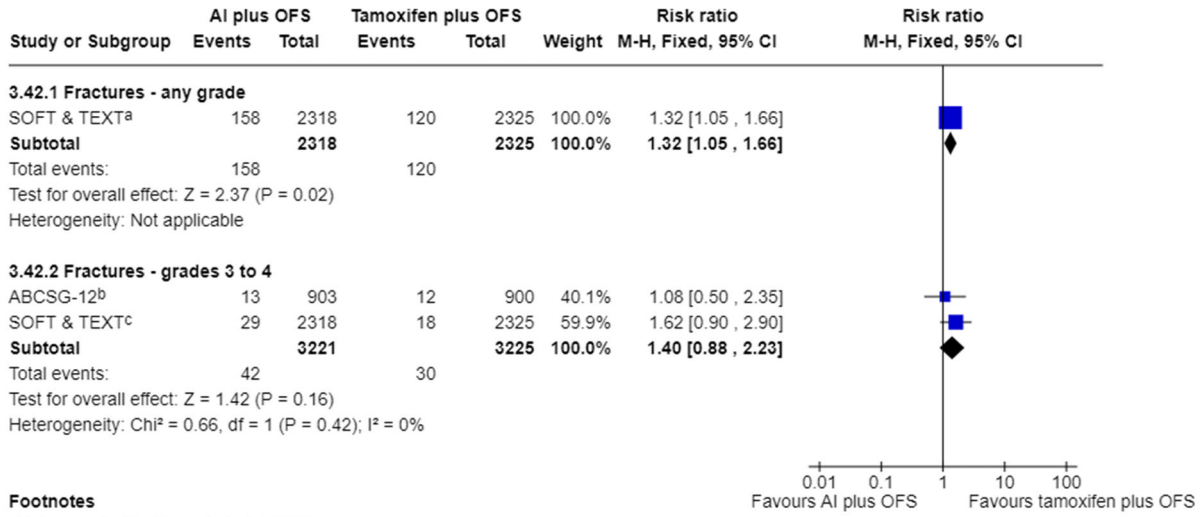
Figure 125 Adverse events – psychosexual: sexual function – 8 years follow-up



Footnotes

[a]Data reported by Francis et al. (2018)

Figure 126 Adverse events – musculoskeletal: fractures – 5 years follow-up



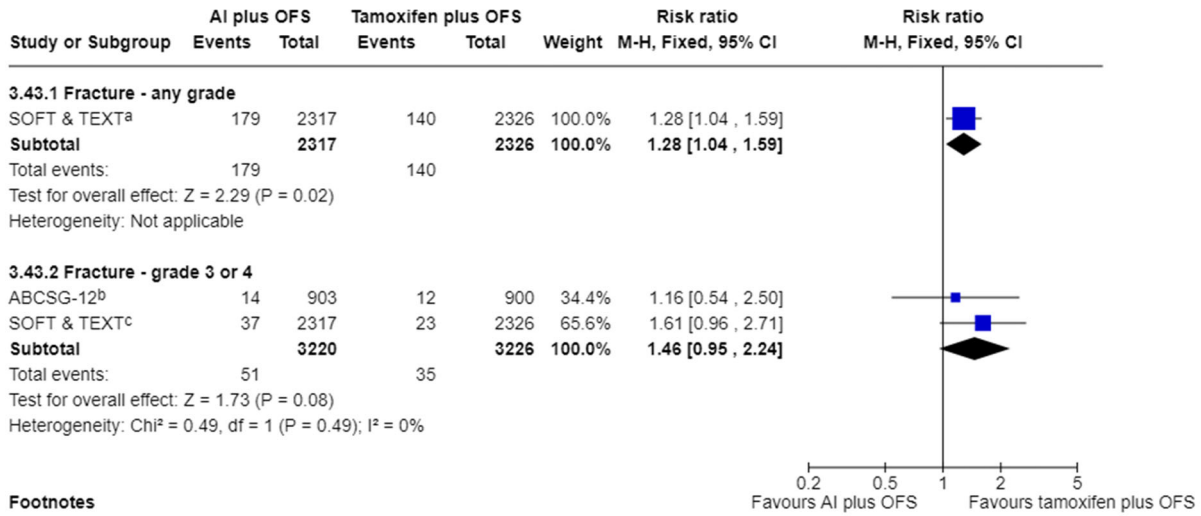
Footnotes

[a]Data reported by Pagani et al. (2014)

[b]Data reported by Gnant et al. (2011); reported as serious adverse event

[c]Data reported by Pagani et al. (2014); adverse event reported as grades 3 to 4

Figure 127 Adverse events – musculoskeletal: fractures – 8 years follow-up



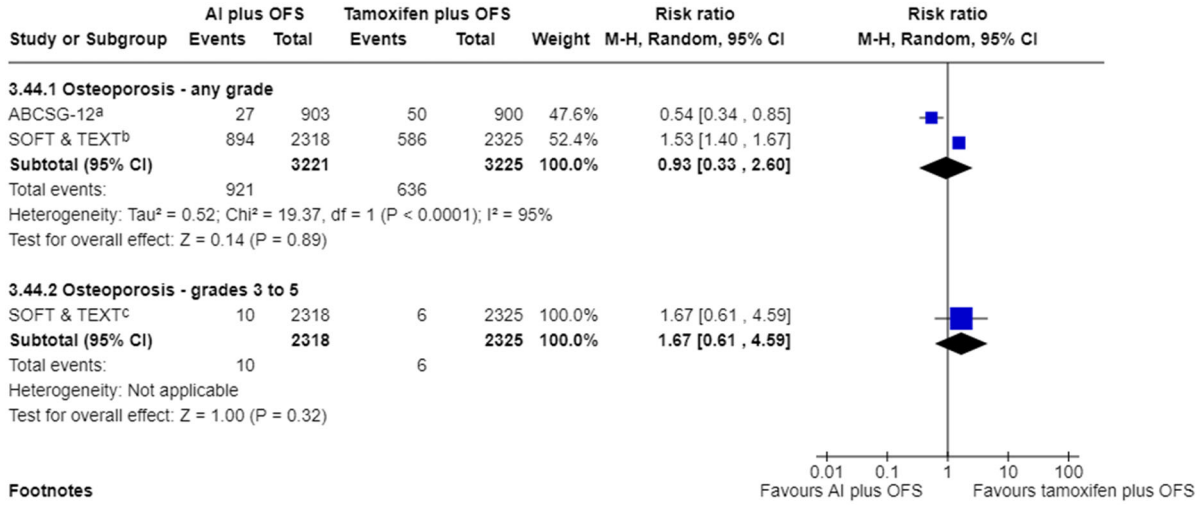
Footnotes

[a]Data reported by Francis et al. (2018)

[b]Data reported by Gnant et al. (2015); reported as serious adverse event

[c]Data reported by Francis et al. (2018); adverse event reported as grades 3 to 4

Figure 128 Adverse events – musculoskeletal: osteoporosis – 5 years follow-up



Footnotes

[a]Data reported by Gnant et al. (2011); grade of adverse event was not reported

[b]Data reported by Pagani et al. (2014); adverse event reported as any grade

[c]Data reported by Pagani et al. (2014)

Figure 129 Adverse events – musculoskeletal: osteoporosis – 8 years follow-up

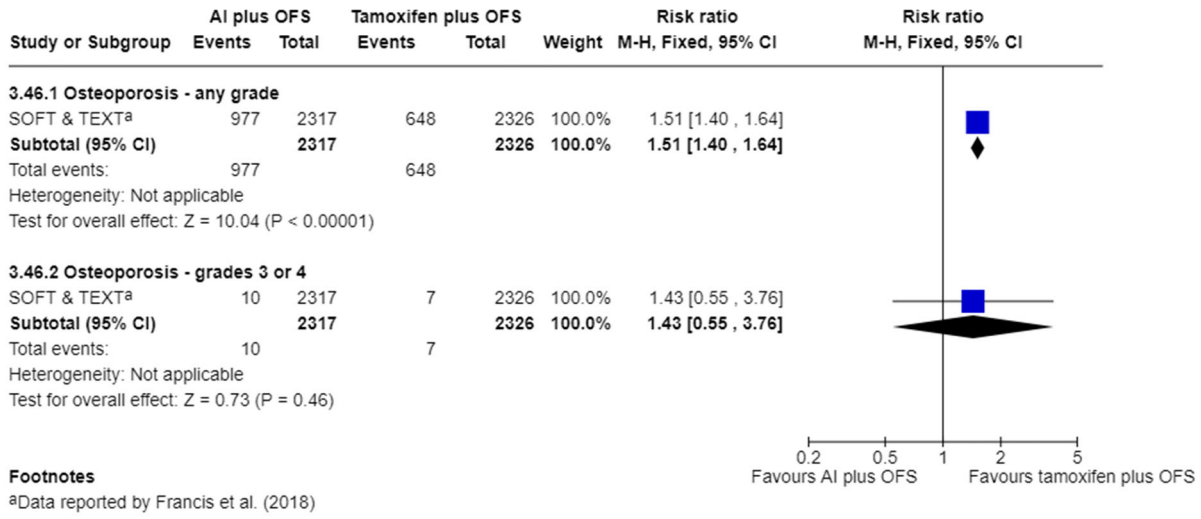
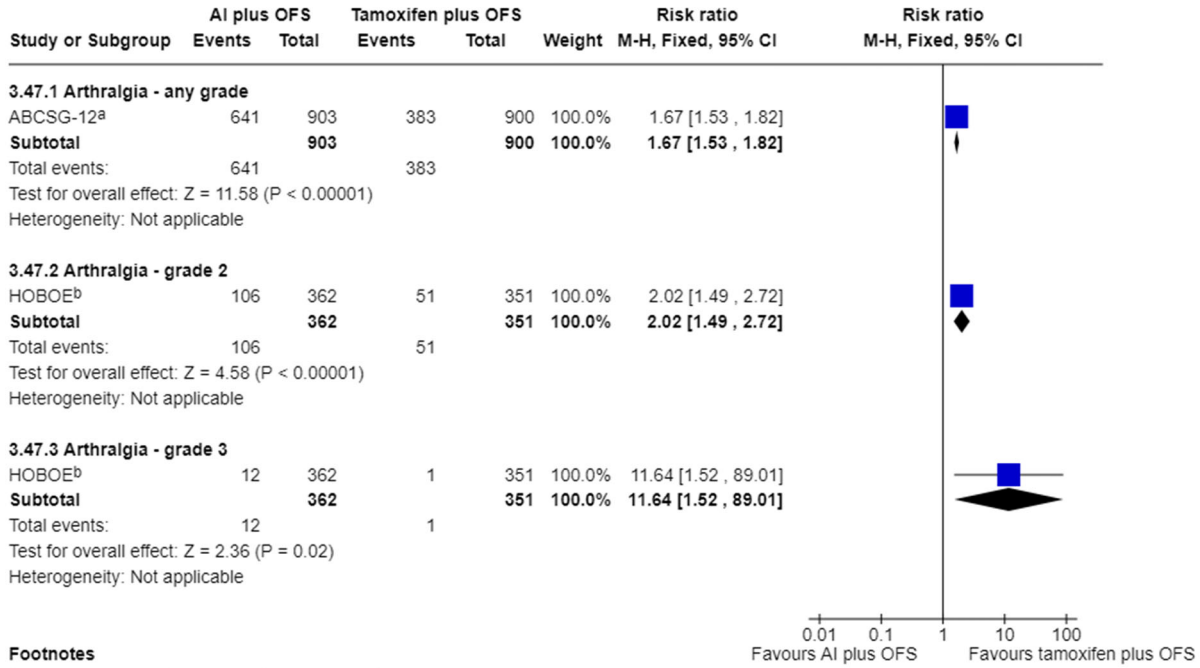


Figure 130 Adverse events – musculoskeletal: arthralgia – 5 years follow-up

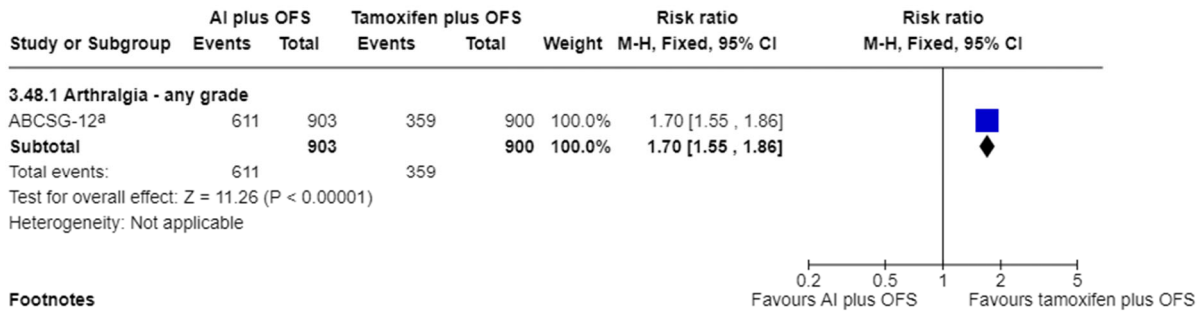


Footnotes

[a]Data reported by Gnant et al. (2011); grade of adverse event was not reported; events included arthralgia, arthropathy and musculoskeletal pain

[b]Data reported by Perrone et al. (2019); events included arthralgia, bone pain and muscle pain

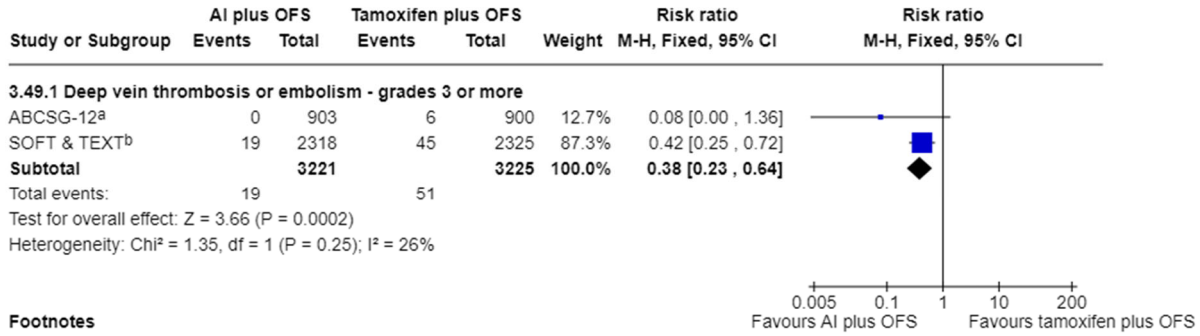
Figure 131 Adverse events – musculoskeletal: arthralgia – 8 years follow-up



Footnotes

[a]Data reported by Gnant et al. (2015); grade of adverse event was not reported; events included arthralgia, arthropathy and bone pain

Figure 132 Adverse events – cardiovascular: deep vein thrombosis or embolism (grades 3 or more) -5 years follow-up

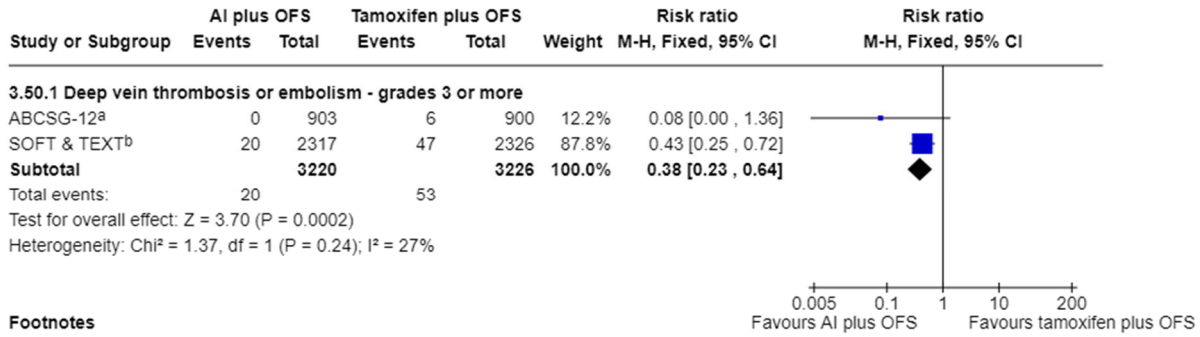


Footnotes

[a]Data reported by Gnant et al. (2011); adverse event reported as serious: deep vein thrombosis

[b]Data reported by Pagani et al. (2014); adverse event reported as grades 3 or 4: thrombosis or embolism

Figure 133 Adverse events – Adverse events – cardiovascular: deep vein thrombosis (grades 3 or more) -8 years follow-up



Footnotes

[a]Data reported by Gnant et al. (2015); adverse event reported as serious: deep vein thrombosis

[b]Data reported by Francis et al. (2018); adverse event reported as grades 3 or 4: thrombosis or embolism

Figure 134 Adverse events – cardiovascular: cardiac ischaemia or infarction (grades 3 or more) – 5 years follow-up

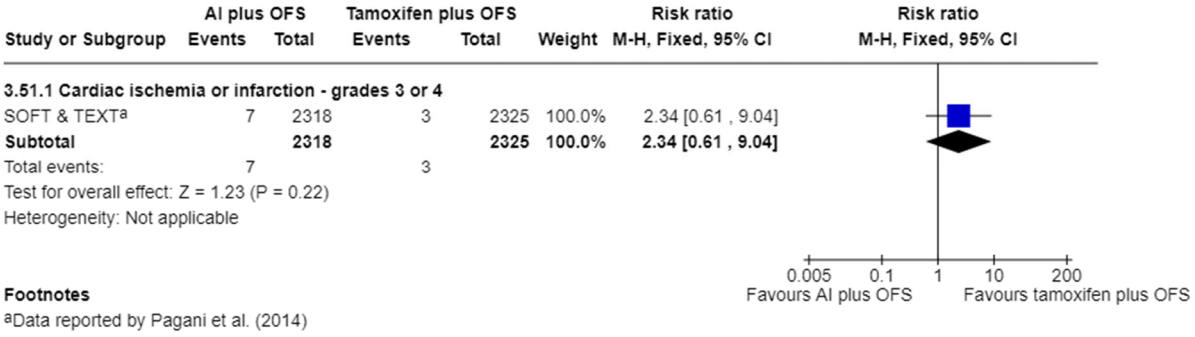
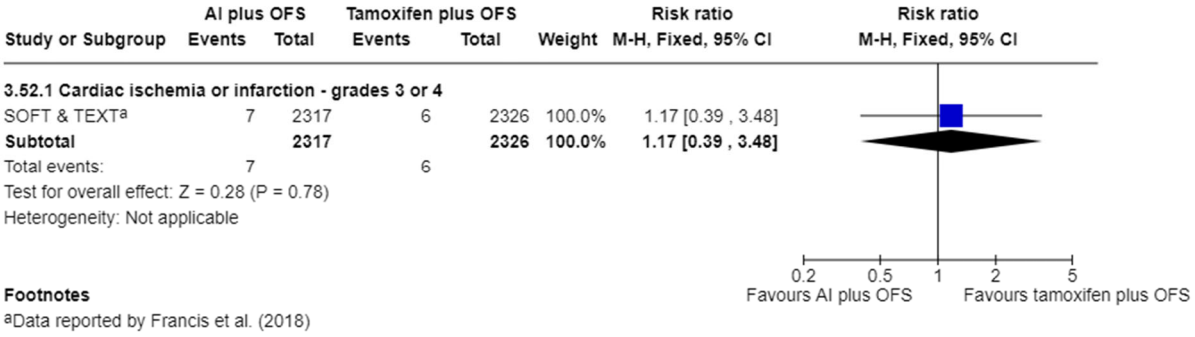


Figure 135 Adverse events – cardiovascular: cardiac ischaemia or infarction (grades 3 or more) – 8 years follow-up



Appendix F – GRADE tables

Ovarian function suppression combined with tamoxifen compared to tamoxifen alone

Overall survival

Table 51 GRADE table for overall survival

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Overall survival - 2.5 to 6 years follow-up												
7 (ABCTCG, ASTRRA, E-3193, SOFT, Sun 2021, Yang 2013, ZIPP)	randomised trials	not serious	not serious	not serious	not serious	none	0/2749 (0.0%)	0/2772 (0.0%)	HR 0.76 (0.62 to 0.92)	Non-calculable	High	CRITICAL
Overall survival – 2.5 to 6 years follow-up sensitivity analysis without study with concurrent chemotherapy (ABCTCG study)												
6 (ASTRRA, E-3193, SOFT, Sun 2021, Yang 2013, ZIPP)	randomised trials	not serious	not serious	not serious	not serious	none	0/2320 (0.0%)	0/2363 (0.0%)	HR 0.72 (0.57 to 0.92)	Non-calculable	High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Overall survival - 2.5 to 6 years follow-up - subgroup analysis by duration of OFS - Duration of OFS: less than 5 years												
4 (ASTRRA, Sun 2021, Yang 2013, ZIPP)	randomised trials	very serious[f]	serious[g]	not serious	not serious	none	0/1135 (0.0%)	0/1178 (0.0%)	HR 0.69 (0.49 to 0.90)	Non-calculable	Very low	CRITICAL
Overall survival - 5 years follow-up - subgroup analysis by duration of OFS - Duration of OFS: 5 years or more												
2 (E-3193[e]: LHRH, E-3193[f]: oophorectomy, SOFT)	randomised trials	not serious	not serious	not serious	serious[a]	none	0/1148 (0.0%)	0/1128 (0.0%)	HR 0.75 (0.53 to 1.06)	Non-calculable	Moderate	IMPORTANT
Overall survival - 2.5 to 6 years follow-up - subgroup analysis by method of OFS - Luteinizing-hormone releasing hormone agonists												
6 (ASTRRA, E-3193, SOFT, Sun 2021, Yang 2013, ZIPP)	randomised trials	not serious	not serious	not serious	not serious	none	0/2211 (0.0%)	0/2251 (0.0%)	HR 0.72 (0.56 to 0.92)	Non-calculable	High	CRITICAL
Overall survival - 5 years follow-up - subgroup analysis by method of OFS - Oophorectomy												
1 (E-3193)	randomised trials	not serious	serious[b]	not serious	very serious[c]	none	0/72 (0.0%)	0/55 (0.0%)	HR 0.71 (0.23 to 2.19)	Non-calculable	Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Overall survival - 5 years follow-up - subgroup analysis by lymph node status - Lymph node positive												
1 (ABCTCG)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	0/429 (0.0%)	0/409 (0.0%)	HR 0.84 (0.59 to 1.20)	Non-calculable	Low	CRITICAL
Overall survival - 5 years follow-up - subgroup analysis by lymph node status - Lymph node negative												
1 (E-3193)	randomised trials	not serious	serious[b]	not serious	very serious[c]	none	0/170 (0.0%)	0/167 (0.0%)	HR 0.84 (0.37 to 1.91)	Non-calculable	Very low	CRITICAL
Overall survival - 5 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: no - RE model (I2 >50%)												
2 (E-3193, SOFT)	randomised trials	not serious	very serious[d]	not serious	serious[a]	none	0/643 (0.0%)	0/643 (0.0%)	HR 1.55 (0.36 to 6.67)	Non-calculable	Very low	CRITICAL
Overall survival - 2.5 to 6 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: yes - FE model												
6 (ABCTCG, ASTRRA, SOFT, Sun 2021, Yang 2013, ZIPP)	randomised trials	not serious	not serious	not serious	not serious	none	0/2106 (0.0%)	0/2129 (0.0%)	HR 0.72 (0.59 to 0.89)	Non-calculable	High	CRITICAL
Overall survival - 8 to 12 years follow-up (OFS duration 5 years; method of OFS: luteinizing-hormone releasing hormone agonists)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	not serious	none	0/1650 (0.0%)	0/1665 (0.0%)	HR 0.78 (0.62 to 0.98)	Non-calculable	High	CRITICAL
Overall survival - 12 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: no												
1 (SOFT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	0/473 (0.0%)	0/476 (0.0%)	HR 0.94 (0.49 to 1.80)	Non-calculable	Low	CRITICAL
Overall survival - 8 to 12 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: yes												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	not serious	none	0/907 (0.0%)	0/1189 (0.0%)	HR 0.76 (0.60 to 0.98)	Non-calculable	High	CRITICAL
Overall survival - 12 years follow-up - subgroup analysis by HER2 status - HER2 negative												
1 (SOFT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	0/868 (0.0%)	0/860 (0.0%)	HR 0.86 (0.65 to 1.14)	Non-calculable	Low	CRITICAL
Overall survival - 12 years follow-up - subgroup analysis by HER2 status - HER2 positive												
1 (SOFT)	randomised trials	not serious	serious[b]	not serious	serious[e]	none	0/119 (0.0%)	0/118 (0.0%)	HR 0.36 (0.16 to 0.79)	Non-calculable	Low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **LHRH:** luteinising hormone-releasing hormone (LHRH) agonists; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level
b. Data was only available from one study, outcome was downgraded one level
c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels
d. I2 was >60%, outcome was downgraded two levels
e. Number of participants was less than 500, outcome was downgraded one level
f. Greater than >50% of the weight in a meta-analysis came from studies at high risk of bias, outcome was downgraded two levels
g. I2 was between 41% and 60%, outcome was downgraded one level

Disease-free survival

Table 52 GRADE table for disease-free survival

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - 5 to 6 years follow-up												
4 (ASTRRA, E-3193, SOFT, Yang 2013)	randomised trials	not serious	not serious	not serious	not serious	none	0/1867 (0.0%)	0/1876 (0.0%)	HR 0.79 (0.66 to 0.94)	Non-calculable	High	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age less than 35 years												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	serious[d]	none	0/210 (0.0%)	0/195 (0.0%)	HR 0.65 (0.43 to 0.99)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age 35 to 39 years												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	serious[a]	none	0/357 (0.0%)	0/397 (0.0%)	HR 0.78 (0.53 to 1.14)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age 40 to 44 years												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	serious[a]	none	0/684 (0.0%)	0/677 (0.0%)	HR 0.79 (0.57 to 1.09)	Non-calculable	Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age 45 to 49 years												
1 (SOFT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	0/301 (0.0%)	0/305 (0.0%)	HR 1.01 (0.60 to 1.71)	Non-calculable	Low	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age 50 years or more												
1 (SOFT)	randomised trials	not serious	serious[b]	not serious	very serious[c]	none	0/98 (0.0%)	0/91 (0.0%)	HR 0.64 (0.30 to 1.38)	Non-calculable	Very low	CRITICAL
Disease-free survival - 5 to 6 years follow-up - subgroup analysis by duration of OFS - Duration of OFS: less than 5 years												
2 (ASTRRA, Yang 2013)	randomised trials	not serious	not serious	not serious	not serious	none	0/682 (0.0%)	0/691 (0.0%)	HR 0.67 (0.48 to 0.94)	Non-calculable	High	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by duration of OFS - Duration of OFS: 5 years or more												
2 (E-3193, SOFT)	randomised trials	not serious	not serious	not serious	serious[a]	none	0/1148 (0.0%)	0/1128 (0.0%)	HR 0.84 (0.68 to 1.04)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 to 6 years follow-up - subgroup analysis by duration of OFS - total												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
4 (ASTRRA, E-3193, SOFT, Yang 2013)	randomised trials	not serious	not serious	not serious	not serious	none	0/1830 (0.0%)	0/1819 (0.0%)	HR 0.79 (0.66 to 0.94)	Non-calculable	High	CRITICAL
Disease-free survival - 5 to 6 years follow-up - subgroup analysis by method of OFS - Luteinizing-hormone releasing hormone agonists												
4 (ASTRRA, E-3193, SOFT, Yang 2013)	randomised trials	not serious	not serious	not serious	not serious	none	0/1758 (0.0%)	0/1764 (0.0%)	HR 0.77 (0.64 to 0.93)	Non-calculable	High	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by method of OFS - Oophorectomy												
1 (E-3193)	randomised trials	not serious	serious[b]	not serious	very serious[c]	none	0/72 (0.0%)	0/55 (0.0%)	HR 1.07 (0.53 to 2.17)	Non-calculable	Very low	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by lymph node status - Lymph node positive												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	serious[a]	none	0/700 (0.0%)	0/714 (0.0%)	HR 0.89 (0.69 to 1.13)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by lymph node status - Lymph node negative												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
3 (ASTRRA, E-3193, SOFT)	randomised trials	not serious	not serious	not serious	not serious	none	0/1120 (0.0%)	0/1114 (0.0%)	HR 0.68 (0.52 to 0.89)	Non-calculable	High	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: no												
2 (E-3193, SOFT)	randomised trials	not serious	not serious	not serious	serious[a]	none	0/643 (0.0%)	0/643 (0.0%)	HR 0.84 (0.58 to 1.22)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 to 6 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: yes												
3 (ASTRRA, SOFT, Yang 2013)	randomised trials	not serious	not serious	not serious	not serious	none	0/954 (0.0%)	0/1233 (0.0%)	HR 0.76 (0.62 to 0.94)	Non-calculable	High	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by HER2 status - HER2 negative												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	serious[a]	none	0/1257 (0.0%)	0/1243 (0.0%)	HR 0.84 (0.68 to 1.04)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by HER2 status - HER2 positive												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	serious[d]	none	0/203 (0.0%)	0/209 (0.0%)	HR 0.44 (0.26 to 0.76)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 to 12 years follow-up (all luteinising -hormone releasing hormone agonists)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
3 (ASTRRA, SOFT, ZIPP)	randomised trials	not serious	not serious	not serious	not serious	none	0/2532 (0.0%)	0/2544 (0.0%)	HR 0.80 (0.71 to 0.90)	Non-calculable	High	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age less than 35 years												
1 (ASTRRA)	randomised trials	not serious	serious[b]	not serious	very serious[c]	none	0/89 (0.0%)	0/83 (0.0%)	HR 0.74 (0.41 to 1.33)	Non-calculable	Very low	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 35 to 39 years												
1 (ASTRRA)	randomised trials	not serious	serious[b]	not serious	very serious[c]	none	0/173 (0.0%)	0/194 (0.0%)	HR 1.00 (0.62 to 1.61)	Non-calculable	Very low	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 40 to 45 years												
1 (ASTRRA)	randomised trials	not serious	serious[b]	not serious	not serious	none	0/373 (0.0%)	0/370 (0.0%)	HR 0.50 (0.34 to 0.73)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 to 12 years follow-up - subgroup analysis by duration of OFS - Duration of OFS: less than 5 years – RE model as I2 >50%												
2 (ASTRRA, ZIPP)	randomised trials	very serious[f]	serious[e]	not serious	not serious	none	0/1517 (0.0%)	0/1526 (0.0%)	HR 0.77 (0.61 to 0.96)	Non-calculable	Very low	CRITICAL
Disease-free survival - 8 to 12 years follow-up - subgroup analysis by duration of OFS - Duration of OFS: 5 years – FE model												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
1 (SOFT)	randomised trials	not serious	serious[b]	not serious	not serious	none	0/1015 (0.0%)	0/1018 (0.0%)	HR 0.82 (0.69 to 0.98)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 12 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: no												
1 (SOFT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	0/473 (0.0%)	0/476 (0.0%)	HR 0.79 (0.58 to 1.08)	Non-calculable	Low	CRITICAL
Disease-free survival - 8 to 12 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: yes												
3 (ASTRRA, SOFT, ZIPP)	randomised trials	not serious	not serious	not serious	not serious	none	0/2059 (0.0%)	0/2068 (0.0%)	HR 0.79 (0.70 to 0.90)	Non-calculable	High	CRITICAL
Disease-free survival - 8 to 12 years follow-up - subgroup analysis by HER2 status - HER2 negative - FE model												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	not serious	none	0/1258 (0.0%)	0/1246 (0.0%)	HR 0.82 (0.69 to 0.97)	Non-calculable	High	CRITICAL
Disease-free survival - 8 to 12 years follow-up - subgroup analysis by HER2 status - HER2 positive - RE model (I2 >50%)												
2 (ASTRRA, SOFT)	randomised trials	not serious	serious[e]	not serious	very serious[c]	none	0/203 (0.0%)	0/210 (0.0%)	HR 0.66 (0.36 to 1.22)	Non-calculable	Very low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. Data was only available from one study, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

d. Number of participants was less than 500, outcome was downgraded one level

e. I2 was between 41% and 60%, outcome was downgraded one level

f. Greater than >50% of the weight in a meta-analysis came from studies at high risk of bias, outcome was downgraded two levels

Breast cancer mortality

Table 53 GRADE table for Breast cancer mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Breast cancer mortality - 12 years follow-up												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	92/1015 (9.1%)	110/1018 (10.8%)	HR 0.83 (0.63 to 1.10)	17 fewer per 1,000 (from 39 fewer to 10 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Local and/or locoregional recurrence

Table 54 GRADE table for Local and/or locoregional recurrence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with tamoxifen**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Local and/or locoregional recurrence - 5 years follow-up												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	not serious	none	30/1650 (1.8%)	55/1665 (3.3%)	RR 0.55 (0.35 to 0.85)	15 fewer per 1,000 (from 21 fewer to 5 fewer)	High	IMPORTANT
Local and/or locoregional recurrence - 8 to 12 years follow-up												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	not serious	none	68/1650 (4.1%)	99/1665 (5.9%)	RR 0.69 (0.51 to 0.94)	18 fewer per 1,000 (from 29 fewer to 4 fewer)	High	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations- none

New contralateral disease

Table 55 GRADE table for new contralateral disease

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
New contralateral disease - 5 years follow-up												
2 (ASTRRA, SOFT)	randomised trials	not serious	not serious	not serious	serious[a]	none	16/1650 (1.0%)	20/1665 (1.2%)	RR 0.81 (0.42 to 1.55)	2 fewer per 1,000 (from 7 fewer to 7 more)	Moderate	IMPORTANT
New contralateral disease - 8 to 12 years follow-up												
2 (ASTRRA, SOFT)	randomised trials	not serious	very serious[b]	not serious	serious[a]	none	30/1650 (1.8%)	37/1665 (2.2%)	RR 0.98 (0.37 to 2.62)	0 fewer per 1,000 (from 14 fewer to 36 more)	Very low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. I2 was between >60%, outcome was downgraded two levels

Adherence to or completion of treatment

Table 56 Summary GRADE table for adherence to or completion of treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with tamoxifen**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adherence to or completion of treatment (treatment completed at 5 years)												
2 (E-3193, SOFT)	randomised trials	not serious	not serious	not serious	not serious	none	570/1185 (48.1%)	491/1185 (41.4%)	RR 1.16 (1.06 to 1.27)	66 more per 1,000 (from 25 more to 112 more)	High	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

N/A

Quality of life

Table 57 GRADE table for quality of life

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - FACT-B (MID +/-8 points)												
1 (E-3193)	randomised trials	not serious	serious[a]	not serious	serious[d]	none	52	64	-	MD 3.42 higher (2.32 lower to 9.16 higher)	Low	CRITICAL
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - FACT-G (MID +/-7 points)												
1 (E-3193)	randomised trials	not serious	serious[a]	not serious	not serious	none	89	95	-	MD 1.5 lower (5.32 lower to 2.32 higher)	Moderate	CRITICAL
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - Breast subscale (MID +/-3 points)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with tamoxifen**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (E-3193)	randomised trials	not serious	serious[a]	not serious	serious[d]	none	53	66	-	MD 2.44 higher (0.21 higher to 4.67 higher)	Low	CRITICAL
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - Menopausal symptoms												
1 (E-3193)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	84	90	-	MD 3.25 lower (6.19 lower to 0.31 lower)	Low	CRITICAL
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - Sexual function												
1 (E-3193)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	69	72	-	MD 1.8 lower (3.45 lower to 0.15 lower)	Low	CRITICAL
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Physical wellbeing												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with tamoxifen**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[c]	none	861	861	-	MD 2 higher (1.5 lower to 5.5 higher)	Low	CRITICAL
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Mood												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[c]	none	861	861	-	MD 2 higher (1 lower to 5 higher)	Low	CRITICAL
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Coping effort												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[c]	none	861	861	-	MD 2 lower (5.5 lower to 1.5 higher)	Low	CRITICAL
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Treatment burden												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[c]	none	861	861	-	MD 1 lower (4.5 lower to 2.5 higher)	Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Quality of life - 5 years follow-up (higher scores indicate better quality of life) - International Breast Cancer Study Group QoL Core Form - Health perception												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[c]	none	861	861	-	MD 1 higher (1.5 lower to 3.5 higher)	Low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. Number of participants was less than 500, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

d. 95% confidence interval crosses one end of a defined MID interval, outcome was downgraded one level

Treatment-related mortality

Table 58 GRADE table for treatment-related mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Treatment-related mortality - cardiac ischaemia or infarction (grade 5)												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/1005 (0.0%)	1/1006 (0.1%)	RR 0.33 (0.01 to 8.18)	1 fewer per 1,000 (from 1 fewer to 7 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Adverse events

Table 59 GRADE table for genitourinary adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Genitourinary - Vaginal dryness - any grade												
1 (SOFT)	randomised trials	not serious	not serious	not serious	not serious	none	500/1005 (49.8%)	421/1006 (41.8%)	RR 1.19 (1.09 to 1.31)	80 more per 1,000 (from 33 more to 130 more)	High	IMPORTANT
Adverse events - Genitourinary - Vaginal dryness - grade 3												
1 (E-3193)	randomised trials	not serious	serious[a]	not serious	very serious[c]	none	1/174 (0.6%)	0/171 (0.0%)	RR 2.95 (0.12 to 71.88)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Very low	IMPORTANT
Adverse events - Genitourinary - Incontinence - any grade												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	185/1005 (18.4%)	162/1006 (16.1%)	RR 1.14 (0.94 to 1.38)	23 more per 1,000 (from 10 fewer to 61 more)	Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Genitourinary - Incontinence - grades 3 to 4												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	5/1005 (0.5%)	6/1006 (0.6%)	RR 0.83 (0.26 to 2.72)	1 fewer per 1,000 (from 4 fewer to 10 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

Table 60 GRADE table for menopausal adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Menopausal symptoms: Vasomotor symptoms (any grade) - RE model (I2 >50%)												
3	randomised trials	not serious	very serious[d]	not serious	serious[b]	None	944/1025 (91.6%)	805/1098 (73.3%)	RR 3.20 (0.34 to 30.09)	1000 more per 1,000 (from 484 fewer to 1000 more)	Very low	IMPORTANT
Adverse events - Menopausal symptoms: Vasomotor symptoms (hot flushes) - grade 3 - RE model (I2 >50%)												
2	randomised trials	not serious	very serious[d]	not serious	not serious	none	161/1179 (13.7%)	84/1177 (7.1%)	RR 2.23 (1.18 to 4.21)	88 more per 1,000 (from 13 more to 229 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - Sleep disturbances or insomnia - any grade												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
1 (SOFT)	randomised trials	not serious	not serious	not serious	serious[b]	none	575/1005 (57.8%)	466/1006 (46.5%)	RR 1.24 (1.13 to 1.35)	111 more per 1,000 (from 60 more to 162 more)	Moderate	IMPORTANT
Adverse events - Menopausal symptoms Insomnia - grades 3 to 4												
2 (E-3193, SOFT)	randomised trials	not serious	serious[e]	not serious	serious[b]	none	46/1179 (3.9%)	31/1177 (2.6%)	RR 1.48 (0.95 to 2.30)	13 more per 1,000 (from 1 fewer to 34 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - Fatigue - any grade												
1 (SOFT)	randomised trials	not serious	not serious	not serious	serious[b]	none	631/1005 (62.8%)	603/1006 (59.9%)	RR 1.05 (0.98 to 1.12)	30 more per 1,000 (from 12 fewer to 72 more)	Moderate	IMPORTANT
Adverse events - Menopausal symptoms - Fatigue - grades 3 to 4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with tamoxifen**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	36/1005 (3.6%)	32/1006 (3.2%)	RR 1.13 (0.71 to 1.80)	4 more per 1,000 (from 9 fewer to 25 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms -Weight gain - any grade												
1 (ZBCSG Trial B)	randomised trials	very serious[f]	serious[a]	not serious	very serious[c]	none	2/20 (10.0%)	5/92 (5.4%)	RR 1.84 (0.38 to 8.82)	46 more per 1,000 (from 34 fewer to 425 more)	Very low	IMPORTANT
Adverse events - Menopausal symptoms Weight gain - grades 3 to 4												
1 (E-3193)	randomised trials	not serious	serious[a]	not serious	very serious[c]	none	6/174 (3.4%)	4/171 (2.3%)	RR 1.47 (0.42 to 5.13)	11 more per 1,000 (from 14 fewer to 97 more)	Very low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

d. I2 was >60%, outcome was downgraded two levels

e. I2 was between 41% and 60%, outcome was downgraded one level

f. Greater than >50% of the weight in a meta-analysis came from studies at high risk of bias, outcome was downgraded two levels

Table 61 GRADE table for glucose intolerance

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with tamoxifen**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Glucose intolerance any grade												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	35/1005 (3.5%)	18/1006 (1.8%)	RR 1.95 (1.11 to 3.41)	17 more per 1,000 (from 2 more to 43 more)	Moderate	IMPORTANT
Adverse events - Glucose intolerance - grades 3 to 4												
2 (E-3193, SOFT)	randomised trials	not serious	not serious	not serious	not serious	none	15/1179 (1.3%)	3/1177 (0.3%)	RR 4.42 (1.39 to 14.07)	9 more per 1,000 (from 1 more to 33 more)	High	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

Table 62 GRADE table for neurocognitive adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Neurocognitive - Depression - any grade												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	522/1005 (51.9%)	469/1006 (46.6%)	RR 1.11 (1.02 to 1.22)	51 more per 1,000 (from 9 more to 103 more)	Moderate	IMPORTANT
Adverse events - Neurocognitive - Depression - grades 3 to 4												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	44/1005 (4.4%)	38/1006 (3.8%)	RR 1.16 (0.76 to 1.77)	6 more per 1,000 (from 9 fewer to 29 more)	Low	IMPORTANT
Adverse events - Neurocognitive -Anxiety - moderate to severe												
1 (Heo 2017)	randomised trials	very serious[d]	serious[a]	not serious	very serious[c]	none	13/32 (40.6%)	14/32 (43.8%)	RR 0.93 (0.52 to 1.65)	31 fewer per 1,000 (from 210 fewer to 284 more)	Very low	IMPORTANT
Adverse events - Neurocognitive Depression and/or anxiety - grade 4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
1 (E-3193)	randomised trials	not serious	serious[a]	not serious	very serious[c]	none	4/174 (2.3%)	4/171 (2.3%)	RR 0.98 (0.25 to 3.87)	0 fewer per 1,000 (from 18 fewer to 67 more)	Very low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

d. Greater than >50% of the weight in a meta-analysis came from studies at high risk of bias, outcome was downgraded two levels

Table 63 GRADE table for psychosexual adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with tamoxifen**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Psychosexual: Sexual function- Decreased libido or dyspareunia- any grade												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	739/1005 (73.5%)	665/1006 (66.1%)	RR 1.11 (1.05 to 1.18)	73 more per 1,000 (from 33 more to 119 more)	Moderate	IMPORTANT
Adverse events - Psychosexual: Sexual function - Changes in libido or dyspareunia- grades 3 to 4												
2 (E-3193, SOFT)	randomised trials	not serious	not serious	not serious	serious[b]	none	23/1179 (2.0%)	14/1177 (1.2%)	RR 1.62 (0.85 to 3.10)	7 more per 1,000 (from 2 fewer to 25 more)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 64 GRADE table for musculoskeletal adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Musculoskeletal - Fractures - any grade												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	54/1005 (5.4%)	49/1006 (4.9%)	RR 1.10 (0.76 to 1.61)	5 more per 1,000 (from 12 fewer to 30 more)	Low	IMPORTANT
Adverse events - Musculoskeletal - Fractures - grades 3 to 4												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	8/1005 (0.8%)	8/1006 (0.8%)	RR 1.00 (0.38 to 2.66)	0 fewer per 1,000 (from 5 fewer to 13 more)	Low	IMPORTANT
Adverse events - Musculoskeletal - Osteoporosis - any grade												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	201/1005 (20.0%)	124/1006 (12.3%)	RR 1.62 (1.32 to 1.99)	76 more per 1,000 (from 39 more to 122 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - Osteoporosis - grades 3 to 4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with tamoxifen	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	3/1005 (0.3%)	1/1006 (0.1%)	RR 3.00 (0.31 to 28.82)	2 more per 1,000 (from 1 fewer to 28 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 65 GRADE table for cardiovascular adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with tamoxifen**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Cardiovascular - thrombosis or embolism grades 3 to 4												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	17/1005 (1.7%)	17/1006 (1.7%)	RR 1.00 (0.51 to 1.95)	0 fewer per 1,000 (from 8 fewer to 16 more)	Low	IMPORTANT
Adverse events - Cardiovascular - cardiac ischaemia or infarction - grades 3 to 4												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	1/1005 (0.1%)	3/1006 (0.3%)	RR 0.33 (0.03 to 3.20)	2 fewer per 1,000 (from 3 fewer to 7 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 66 GRADE table for other cancers

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with tamoxifen**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Other cancers												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	36/1014 (3.6%)	39/1018 (3.8%)	RR 0.93 (0.59 to 1.45)	3 fewer per 1,000 (from 16 fewer to 17 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Ovarian function suppression combined with an aromatase inhibitor compared to tamoxifen alone

Overall survival

Table 67 GRADE table for overall survival

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Overall survival - 5 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/1014 (0.0%)	0/1018 (0.0%)	HR 0.97 (0.68 to 1.39)	Non-calculable	Low	CRITICAL
Overall survival - 5 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: no												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/470 (0.0%)	0/476 (0.0%)	HR 4.03 (0.86 to 18.94)	Non-calculable	Low	CRITICAL
Overall survival - 5 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: yes												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/544 (0.0%)	0/542 (0.0%)	HR 0.87 (0.59 to 1.28)	Non-calculable	Low	CRITICAL
Overall survival - 12 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/1014 (0.0%)	0/1018 (0.0%)	HR 0.80 (0.62 to 1.04)	Non-calculable	Low	CRITICAL
Overall survival - 12 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: no												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/470 (0.0%)	0/476 (0.0%)	HR 0.79 (0.40 to 1.56)	Non-calculable	Low	CRITICAL
Overall survival - 12 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: yes												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/544 (0.0%)	0/542 (0.0%)	HR 0.80 (0.61 to 1.04)	Non-calculable	Low	CRITICAL
Overall survival - 12 years follow-up - subgroup analysis by HER2 status - HER2 negative												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/858 (0.0%)	0/860 (0.0%)	HR 0.77 (0.57 to 1.04)	Non-calculable	Low	CRITICAL
Overall survival - 12 years follow-up - subgroup analysis by HER2 status - HER2 positive												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	very serious[c]	none	0/130 (0.0%)	0/118 (0.0%)	HR 0.83 (0.46 to 1.50)	Non-calculable	Very low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

Disease-free survival

Table 68 GRADE table for disease-free survival

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - 5 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	0/1014 (0.0%)	0/1018 (0.0%)	HR 0.68 (0.53 to 0.87)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: no												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/470 (0.0%)	0/476 (0.0%)	HR 0.61 (0.36 to 1.03)	Non-calculable	Low	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: yes												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	0/544 (0.0%)	0/542 (0.0%)	HR 0.70 (0.53 to 0.92)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age less than 35 years												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[d]	none	0/117 (0.0%)	0/112 (0.0%)	HR 0.52 (0.31 to 0.87)	Non-calculable	Low	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 35 to 39 years												

1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[d]	none	0/196 (0.0%)	0/203 (0.0%)	HR 0.66 (0.44 to 0.99)	Non-calculable	Low	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 40 to 44 years												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/289 (0.0%)	0/307 (0.0%)	HR 0.89 (0.60 to 1.33)	Non-calculable	Low	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 45 to 49 years												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	0/304 (0.0%)	0/305 (0.0%)	HR 0.57 (0.34 to 0.95)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 50 years or more												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[d]	none	0/108 (0.0%)	0/91 (0.0%)	HR 0.38 (0.17 to 0.84)	Non-calculable	Low	CRITICAL
Disease-free survival - 12 years follow-up (OFS duration 5 years; method of OFS: luteinising-hormone releasing hormone agonists)												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	0/1014 (0.0%)	0/1018 (0.0%)	HR 0.69 (0.57 to 0.83)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 12 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: no												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	0/470 (0.0%)	0/476 (0.0%)	HR 0.59 (0.42 to 0.82)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 12 years follow-up - subgroup analysis by prior use of chemotherapy - Prior chemotherapy: yes												

1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	0/544 (0.0%)	0/542 (0.0%)	HR 0.73 (0.58 to 0.91)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 12 years follow-up - subgroup analysis by HER2 status - HER2 negative												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	0/858 (0.0%)	0/860 (0.0%)	HR 0.62 (0.50 to 0.76)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 12 years follow-up - subgroup analysis by HER2 status - HER2 positive												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	very serious[c]	none	0/130 (0.0%)	0/118 (0.0%)	HR 0.88 (0.56 to 1.38)	Non-calculable	Very low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

d. Number of participants was less than 500, outcome was downgraded one level

Breast cancer mortality

Table 69 GRADE table for breast cancer mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Breast cancer mortality - 12 years follow-up												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	85/1014 (8.4%)	110/1018 (10.8%)	HR 0.77 (0.58 to 1.02)	24 fewer per 1,000 (from 44 fewer to 2 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Local and/or locoregional recurrence

Table 70 GRADE table for local and/or locoregional recurrence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Local and/or locoregional recurrence - 12 years follow-up												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	36/1014 (3.6%)	66/1018 (6.5%)	RR 0.55 (0.37 to 0.81)	29 fewer per 1,000 (from 41 fewer to 12 fewer)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

New contralateral disease

Table 71 GRADE table for new contralateral disease

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
New contralateral disease - 12 years follow-up												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	not serious	none	16/1014 (1.6%)	32/1018 (3.1%)	RR 0.50 (0.28 to 0.91)	16 fewer per 1,000 (from 23 fewer to 3 fewer)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

Adherence to or completion of treatment

Table 72 GRADE table for adherence to or completion of treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adherence to or completion of treatment (treatment completed at 8 years)												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	798/1014 (78.7%)	771/1018 (75.7%)	RR 1.04 (0.99 to 1.09)	30 more per 1,000 (from 8 fewer to 68 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Quality of life

No evidence identified for this outcome.

Treatment-related mortality

Table 73 GRADE table for treatment-related mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Treatment-related mortality												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	0/2317 (0.0%)	1/1005 (0.1%)	RR 0.14 (0.01 to 3.55)	1 fewer per 1,000 (from 1 fewer to 3 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Adverse events

Table 74 GRADE table for genitourinary adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Genitourinary - Vaginal dryness - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	1245/2317 (53.7%)	426/1005 (42.4%)	RR 1.27 (1.17 to 1.38)	114 more per 1,000 (from 72 more to 161 more)	Moderate	IMPORTANT
Adverse events - Genitourinary - Incontinence - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	317/2317 (13.7%)	166/1005 (16.5%)	RR 0.83 (0.70 to 0.98)	28 fewer per 1,000 (from 50 fewer to 3 fewer)	Moderate	IMPORTANT
Adverse events - Genitourinary - Incontinence - grades 3 to 4												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	9/2317 (0.4%)	6/1005 (0.6%)	RR 0.65 (0.23 to 1.82)	2 fewer per 1,000 (from 5 fewer to 5 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 75 GRADE table for menopausal adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Menopausal symptoms - Vasomotor symptoms (hot flushes)- any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	2141/2317 (92.4%)	808/1005 (80.4%)	RR 1.15 (1.11 to 1.19)	121 more per 1,000 (from 88 more to 153 more)	Moderate	IMPORTANT
Adverse events - Menopausal symptoms - Vasomotor symptoms (hot flushes) - grades 3 to 4												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	234/2317 (10.1%)	78/1005 (7.8%)	RR 1.30 (1.02 to 1.66)	23 more per 1,000 (from 2 more to 51 more)	Moderate	IMPORTANT
Adverse events - Menopausal symptoms - Sleep disturbances - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	1375/2317 (59.3%)	470/1005 (46.8%)	RR 1.27 (1.18 to 1.37)	126 more per 1,000 (from 84 more to 173 more)	Moderate	IMPORTANT
Adverse events - Menopausal symptoms - Insomnia - grades 3 to 4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	89/2317 (3.8%)	30/1005 (3.0%)	RR 1.29 (0.86 to 1.93)	9 more per 1,000 (from 4 fewer to 28 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - Fatigue - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	1450/2317 (62.6%)	612/1005 (60.9%)	RR 1.03 (0.97 to 1.09)	18 more per 1,000 (from 18 fewer to 55 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - Fatigue - grades 3 to 4												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	75/2317 (3.2%)	34/1005 (3.4%)	RR 0.96 (0.64 to 1.43)	1 fewer per 1,000 (from 12 fewer to 15 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 76 GRADE table for glucose intolerance

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Glucose intolerance - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	63/2317 (2.7%)	18/1005 (1.8%)	RR 1.52 (0.90 to 2.55)	9 more per 1,000 (from 2 fewer to 28 more)	Low	IMPORTANT
Adverse events - Glucose intolerance - grades 3 to 4												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	15/2317 (0.6%)	4/1005 (0.4%)	RR 1.63 (0.54 to 4.89)	3 more per 1,000 (from 2 fewer to 15 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 77 GRADE table for neurocognitive adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Neurocognitive - Depression - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	1197/2317 (51.7%)	476/1005 (47.4%)	RR 1.09 (1.01 to 1.18)	43 more per 1,000 (from 5 more to 85 more)	Moderate	IMPORTANT
Adverse events - Neurocognitive - Depression - grades 3 to 4												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	95/2317 (4.1%)	41/1005 (4.1%)	RR 1.01 (0.70 to 1.44)	0 fewer per 1,000 (from 12 fewer to 18 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 78 GRADE table for psychosexual adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Psychosexual: Sexual function - Decreased libido - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	1056/2317 (45.6%)	434/1005 (43.2%)	RR 1.06 (0.97 to 1.15)	26 more per 1,000 (from 13 fewer to 65 more)	Low	IMPORTANT
Adverse events - Psychosexual: Sexual function - Dyspareunia - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	733/2317 (31.6%)	242/1005 (24.1%)	RR 1.31 (1.16 to 1.49)	75 more per 1,000 (from 39 more to 118 more)	Moderate	IMPORTANT
Adverse events - Psychosexual: Sexual function - Dyspareunia - grades 3 to 4												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	56/2317 (2.4%)	16/1005 (1.6%)	RR 1.52 (0.88 to 2.63)	8 more per 1,000 (from 2 fewer to 26 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 79 GRADE table for musculoskeletal adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Musculoskeletal - Fractures - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	179/2317 (7.7%)	53/1005 (5.3%)	RR 1.46 (1.09 to 1.97)	24 more per 1,000 (from 5 more to 51 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - Fractures - grades 3 to 4												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	37/2317 (1.6%)	8/1005 (0.8%)	RR 2.01 (0.94 to 4.29)	8 more per 1,000 (from 0 fewer to 26 more)	Low	IMPORTANT
Adverse events - Musculoskeletal - Osteoporosis - any grade												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	977/2317 (42.2%)	138/1005 (13.7%)	RR 3.07 (2.62 to 3.61)	284 more per 1,000 (from 222 more to 358 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - Osteoporosis - grades 3 to 4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	10/2317 (0.4%)	1/1005 (0.1%)	RR 4.34 (0.56 to 33.84)	3 more per 1,000 (from 0 fewer to 33 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 80 GRADE table for cardiovascular adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Cardiovascular - thrombosis or embolism - Thrombosis or embolism - grades 3 to 4												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	20/2317 (0.9%)	17/1005 (1.7%)	RR 0.51 (0.27 to 0.97)	8 fewer per 1,000 (from 12 fewer to 1 fewer)	Moderate	IMPORTANT
Adverse events - Cardiovascular - cardiac ischaemia or infarction (grades 3 or more) - Cardiac ischaemia or infarction - grades 3 to 4												
1 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	7/2317 (0.3%)	4/1005 (0.4%)	RR 0.76 (0.22 to 2.59)	1 fewer per 1,000 (from 3 fewer to 6 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Table 81 GRADE table for other cancers

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Other cancers												
1 (SOFT)	randomised trials	not serious	serious[a]	not serious	serious[b]	none	33/1014 (3.3%)	39/1018 (3.8%)	RR 0.85 (0.54 to 1.34)	6 fewer per 1,000 (from 18 fewer to 13 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

Ovarian function suppression combined with an aromatase inhibitor compared to ovarian function suppression combined with tamoxifen

Overall survival

Table 82 GRADE table for overall survival

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Overall survival - 5 years follow-up (all with method of OFS: luteinizing-hormone releasing hormone agonists)												
3 (ABCSG-12, HOBOE, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	0/3605 (0.0%)	0/3598 (0.0%)	HR 1.16 (0.75 to 1.81)	Non-calculable	Very low	CRITICAL
Overall survival - 5 years follow-up – subgroup analysis by duration of OFS: less than 5 years												
1 (ABCSG-12)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/903 (0.0%)	0/900 (0.0%)	HR 1.75 (1.08 to 2.83)	Non-calculable	Moderate	CRITICAL
Overall survival - 5 years follow-up – subgroup analysis by duration of OFS: 5 years												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (HOBOE, SOFT and TEXT)	randomised trials	not serious	serious[d]	not serious	serious[b]	none	0/2702 (0.0%)	0/2698 (0.0%)	HR 1.06 (0.82 to 1.38)	Non-calculable	Low	CRITICAL
Overall survival – 5 years follow-up – subgroup analysis by use of chemotherapy – Chemotherapy: yes – RE model (I2 >50%)												
2 (ABCSG-12, HOBOE)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	0/1259 (0.0%)	0/1254 (0.0%)	HR 1.10 (0.41 to 2.96)	Non-calculable	Very low	CRITICAL
Overall survival - 8 to 12 years follow-up (all with method of OFS: luteinizing-hormone releasing hormone agonists)												
2 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	0/3249 (0.0%)	0/3244 (0.0%)	HR 1.19 (0.69 to 2.05)	Non-calculable	Very low	CRITICAL
Overall survival - 8 to 12 years follow-up – sensitivity analysis without study with concurrent chemotherapy (TEXT study)												
2 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	0/2443 (0.0%)	0/2443 (0.0%)	HR 1.24 (0.78 to 1.97)	Non-calculable	Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Overall survival - 8 to 12 years follow-up – subgroup analysis by duration of OFS: less than 5 years												
1 (ABCSG-12)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/903 (0.0%)	0/900 (0.0%)	HR 1.63 (1.05 to 2.53)	Non-calculable	Moderate	CRITICAL
Overall survival - 8 to 12 years follow-up – subgroup analysis by duration of OFS: 5 years												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/2346 (0.0%)	0/2344 (0.0%)	HR 0.93 (0.78 to 1.11)	Non-calculable	Low	CRITICAL
Overall survival - 12 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: no - FE model												
1 (SOFT and TEXT)	randomised trials	not serious	not serious	not serious	serious[b]	none	0/996 (0.0%)	0/1000 (0.0%)	HR 0.90 (0.58 to 1.39)	Non-calculable	Moderate	CRITICAL
Overall survival - 8 to 12 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: yes - RE model (I2 >50%)												
2 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	0/2253 (0.0%)	0/2244 (0.0%)	HR 1.19 (0.70 to 2.04)	Non-calculable	Very low	CRITICAL
Overall survival - 8 years follow-up - subgroup analysis by HER2 status - HER2 negative												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/2011 (0.0%)	0/2024 (0.0%)	HR 0.70 (0.60 to 0.82)	Non-calculable	Moderate	CRITICAL
Overall survival - 8 years follow-up - subgroup analysis by HER2 status - HER2 positive												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/298 (0.0%)	0/280 (0.0%)	HR 1.18 (0.80 to 1.74)	Non-calculable	Low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. I2 was >60%, outcome was downgraded two levels

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. Data was only available from one study, outcome was downgraded one level

d. I2 was between 40% and 60%,, outcome was downgraded one level

Disease-free survival

Table 83 GRADE table for disease-free survival

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - 5 years follow-up (all with method of OFS: luteinizing-hormone releasing hormone agonists)												
3 (ABCSG-12, HOBOE, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	0/3605 (0.0%)	0/3598 (0.0%)	HR 0.82 (0.63 to 1.08)	Non-calculable	Very low	CRITICAL
Disease-free survival - 5 years follow-up – sensitivity analysis without study with concurrent chemotherapy (TEXT study)												
3 (ABCSG-12, HOBOE, SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/2799 (0.0%)	0/2797 (0.0%)	HR 0.84 (0.64 to 1.10)	Non-calculable	Low	CRITICAL
Disease-free survival - 5 years follow-up – subgroup analysis by duration of OFS: less than 5 years (RE model to match main analysis)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
1 (ABCSG-12)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/903 (0.0%)	0/900 (0.0%)	HR 1.08 (0.81 to 1.44)	Non-calculable	Low	CRITICAL
Disease-free survival - 5 years follow-up – subgroup analysis by duration of OFS: 5 years – (RE model to match main analysis)												
2 (HOBOE, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	not serious	none	0/2702 (0.0%)	0/2698 (0.0%)	HR 0.72 (0.61 to 0.84)	Non-calculable	High	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age less than 35 years												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	very serious[d]	none	0/231 (0.0%)	0/239 (0.0%)	HR 0.84 (0.57 to 1.24)	Non-calculable	Very low	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age 35 to 39 years												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/419 (0.0%)	0/373 (0.0%)	HR 0.67 (0.46 to 0.97)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age 40 to 44 years												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/748 (0.0%)	0/775 (0.0%)	HR 0.73 (0.53 to 1.00)	Non-calculable	Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age 45 to 49 years												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/731 (0.0%)	0/767 (0.0%)	HR 0.71 (0.48 to 1.05)	Non-calculable	Low	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by age - Age 50 years or more												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	very serious[d]	none	0/217 (0.0%)	0/190 (0.0%)	HR 0.49 (0.24 to 1.00)	Non-calculable	Very low	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by lymph node status - Lymph node positive												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/984 (0.0%)	0/994 (0.0%)	HR 0.79 (0.64 to 0.98)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by lymph node status - Lymph node negative												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/1362 (0.0%)	0/1350 (0.0%)	HR 0.60 (0.45 to 0.80)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: no												
1 (SOFT and TEXT)	randomised trials	not serious	not serious	not serious	not serious	none	0/996 (0.0%)	0/1000 (0.0%)	HR 0.60 (0.41 to 0.88)	Non-calculable	High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Disease-free survival - 5 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: yes - RE model (I2 >50%)												
3 (ABCSG-12, HOBOE, SOFT and TEXT)	randomised trials	not serious	serious[e]	not serious	not serious	none	0/2609 (0.0%)	0/2598 (0.0%)	HR 0.84 (0.65 to 1.08)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by HER2 status - HER2 negative												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/2017 (0.0%)	0/2021 (0.0%)	HR 0.63 (0.52 to 0.76)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 5 years follow-up - subgroup analysis by HER2 status - HER2 positive												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/288 (0.0%)	0/279 (0.0%)	HR 1.25 (0.80 to 1.92)	Non-calculable	Low	CRITICAL
Disease-free survival - 8 to 12 years follow-up (all with method of OFS: luteinizing-hormone releasing hormone agonists)												
2 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	0/3249 (0.0%)	0/3244 (0.0%)	HR 0.93 (0.66 to 1.32)	Non-calculable	Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - 8 years follow-up sensitivity analysis without study with concurrent chemotherapy (TEXT study)												
2 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	0/2443 (0.0%)	0/2443 (0.0%)	HR 0.95 (0.70 to 1.30)	Non-calculable	Very low	CRITICAL
Disease-free survival - 8 to 12 years follow-up – subgroup analysis by duration of OFS: less than 5 years												
1 (ABCSG-12)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/903 (0.0%)	0/900 (0.0%)	HR 1.13 (0.88 to 1.45)	Non-calculable	Low	CRITICAL
Disease-free survival - 8 to 12 years follow-up – subgroup analysis by duration of OFS: 5 years												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/2346 (0.0%)	0/2344 (0.0%)	HR 0.79 (0.70 to 0.90)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age less than 35 years												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	very serious[d]	none	0/231 (0.0%)	0/239 (0.0%)	HR 0.86 (0.60 to 1.23)	Non-calculable	Very low	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 35 to 39 years												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/419 (0.0%)	0/373 (0.0%)	HR 0.83 (0.61 to 1.13)	Non-calculable	Low	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 40 to 44 years												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/748 (0.0%)	0/775 (0.0%)	HR 0.75 (0.58 to 0.97)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 45 to 49 years												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/730 (0.0%)	0/767 (0.0%)	HR 0.71 (0.52 to 0.97)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by age - Age 50 years or more												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	very serious[d]	none	0/218 (0.0%)	0/190 (0.0%)	HR 0.62 (0.35 to 1.09)	Non-calculable	Very low	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by lymph node status - Lymph node positive												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/984 (0.0%)	0/996 (0.0%)	HR 0.81 (0.67 to 0.97)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by lymph node status - Lymph node negative												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/1362 (0.0%)	0/1348 (0.0%)	HR 0.72 (0.57 to 0.91)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: no - FE model												
2 (SOFT and TEXT)	randomised trials	not serious	not serious	not serious	not serious	none	0/996 (0.0%)	0/1000 (0.0%)	HR 0.73 (0.55 to 0.97)	Non-calculable	High	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by use of chemotherapy - Chemotherapy: yes - RE model (I2 >50%)												
2 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	0/2253 (0.0%)	0/2244 (0.0%)	HR 0.93 (0.66 to 1.32)	Non-calculable	Very low	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by HER2 status - HER2 negative												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	0/2011 (0.0%)	0/2024 (0.0%)	HR 0.70 (0.60 to 0.82)	Non-calculable	Moderate	CRITICAL
Disease-free survival - 8 years follow-up - subgroup analysis by HER2 status - HER2 positive												
1 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	0/298 (0.0%)	0/280 (0.0%)	HR 1.18 (0.80 to 1.74)	Non-calculable	Low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. I2 was >60%, outcome was downgraded two levels

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. Data was only available from one study, outcome was downgraded one level

d. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

e. I2 was between 41% and 60%, outcome was downgraded one level

Breast cancer mortality

Table 84 GRADE table for breast cancer mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Breast cancer mortality - 5 years follow-up												
1 (ABCSG-12)	randomised trials	not serious	serious[b]	not serious	serious[d]	none	0/97 (0.0%)	0/88 (0.0%)	HR 2.00 (1.23 to 3.25)	Not calculable	Low	IMPORTANT
Breast cancer mortality - 8 to 12 years follow-up												
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[a]	none	0/2480 (0.0%)	0/2461 (0.0%)	HR 0.90 (0.74 to 1.09)	Not calculable	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. Data was only available from one study, outcome was downgraded one level

c. I2 was between 41% and 60%, outcome was downgraded one level

d. Number of participants was less than 500, outcome was downgraded one level

Local and/or locoregional recurrence

Table 85 GRADE table for local and/or locoregional recurrence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Local and/or locoregional recurrence - 5 years follow-up												
4 (ABCSG-12, HOBOE, SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	68/3605 (1.9%)	91/3598 (2.5%)	RR 0.82 (0.50 to 1.36)	5 fewer per 1,000 (from 13 fewer to 9 more)	Low	IMPORTANT
Local and/or locoregional recurrence - 8 to 12 years follow-up												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	110/3249 (3.4%)	153/3244 (4.7%)	RR 0.75 (0.52 to 1.10)	12 fewer per 1,000 (from 23 fewer to 5 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. I2 was between 41% and 60%, outcome was downgraded one level

New contralateral disease

Table 86 GRADE table for new contralateral disease

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
New contralateral disease - 5 years follow-up												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
4 (ABCSG-12, HOBOE, SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	not serious	none	20/3605 (0.6%)	43/3598 (1.2%)	RR 0.46 (0.27 to 0.79)	6 fewer per 1,000 (from 9 fewer to 3 fewer)	Moderate	IMPORTANT
New contralateral disease - 8 to 12 years follow-up												
4 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	serious[a]	none	45/3249 (1.4%)	61/3244 (1.9%)	RR 0.74 (0.50 to 1.08)	5 fewer per 1,000 (from 9 fewer to 2 more)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. I2 was between 41% and 60%, outcome was downgraded one level

Adherence to or completion of treatment

Table 87 GRADE table for adherence to or completion of treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Adherence to or completion of treatment (treatment completed at 5 years)												
3 (HOBOE, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	1490/2702 (55.1%)	1526/2698 (56.6%)	RR 1.06 (0.83 to 1.34)	34 more per 1,000 (from 96 fewer to 192 more)	Very low	IMPORTANT
Adherence to or completion of treatment (treatment completed at 8 years)												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	1901/2346 (81.0%)	2027/2344 (86.5%)	RR 0.94 (0.91 to 0.96)	52 fewer per 1,000 (from 78 fewer to 35 fewer)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. I2 was >60%, outcome was downgraded two levels

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. Data was only available from one study, outcome was downgraded one level

Quality of life

No evidence identified for this outcome.

Adverse events

Table 88 GRADE table for genitourinary adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Genitourinary - 5 years follow-up - Vaginal dryness - any grade												
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	not serious	none	1214/2318 (52.4%)	1101/2325 (47.4%)	RR 1.11 (1.04 to 1.17)	52 more per 1,000 (from 19 more to 81 more)	Moderate	IMPORTANT
Adverse events - Genitourinary - 5 years follow-up - Vaginal dryness - grade 2												
1 (HOBOE)	randomised trials	not serious	serious[b]	not serious	not serious	none	31/362 (8.6%)	9/351 (2.6%)	RR 3.34 (1.61 to 6.91)	60 more per 1,000 (from 16 more to 152 more)	Moderate	IMPORTANT
Adverse events - Genitourinary - 8 years follow-up (any grade) - Vaginal dryness - any grade												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	not serious	none	1245/2317 (53.7%)	1144/2326 (49.2%)	RR 1.09 (1.03 to 1.16)	44 more per 1,000 (from 15 more to 79 more)	Moderate	IMPORTANT
Adverse events - Genitourinary - 5 years follow-up - Incontinence - any grade												
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	not serious	none	304/2318 (13.1%)	414/2325 (17.8%)	RR 0.74 (0.64 to 0.84)	46 fewer per 1,000 (from 64 fewer to 28 fewer)	Moderate	IMPORTANT
Adverse events - Genitourinary - 5 years follow-up (grades 3 or more) - Incontinence - grades 3 to 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	6/2318 (0.3%)	7/2325 (0.3%)	RR 0.86 (0.29 to 2.55)	0 fewer per 1,000 (from 2 fewer to 5 more)	Low	IMPORTANT
Adverse events - Genitourinary - 8 years follow-up (any grade) - Incontinence - any grade												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	not serious	none	317/2317 (13.7%)	433/2326 (18.6%)	RR 0.73 (0.64 to 0.84)	50 fewer per 1,000 (from 67 fewer to 30 fewer)	Moderate	IMPORTANT
Adverse events - Genitourinary - 8 years follow-up (grades 3 or more) - Incontinence - grades 3 or 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	9/2317 (0.4%)	9/2326 (0.4%)	RR 1.00 (0.40 to 2.52)	0 fewer per 1,000 (from 2 fewer to 6 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. Data was only available from one study, outcome was downgraded one level

Table 89 GRADE table for menopausal adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Menopausal symptoms - 5 years follow-up (any grade or grade 2) - Vasomotor symptoms (hot flushes) - any grade												
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	not serious	none	2149/3221 (66.7%)	2200/3225 (68.2%)	RR 0.98 (0.96 to 1.00)	14 fewer per 1,000 (from 27 fewer to 0 fewer)	High	IMPORTANT
Adverse events - Menopausal symptoms - 5 years follow-up - Vasomotor symptoms (hot flushes) - grade 2												
1 (HOBOE)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	73/362 (20.2%)	82/351 (23.4%)	RR 0.86 (0.65 to 1.14)	33 fewer per 1,000 (from 82 fewer to 33 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 5 years follow-up - Vasomotor symptoms (hot flushes) - grades 3 to 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	232/2318 (10.0%)	279/2325 (12.0%)	RR 0.83 (0.71 to 0.98)	20 fewer per 1,000 (from 35 fewer to 2 fewer)	Moderate	IMPORTANT
Adverse events - Menopausal symptoms - 8 years follow-up (any grade) - Vasomotor symptoms (hot flushes) - any grade												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	2141/2317 (92.4%)	2175/2326 (93.5%)	RR 0.99 (0.97 to 1.00)	9 fewer per 1,000 (from 28 fewer to 0 fewer)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 8 years follow-up (grades 3 or more) - Vasomotor symptoms (hot flushes) - grades 3 or 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	234/2317 (10.1%)	284/2326 (12.2%)	RR 0.83 (0.70 to 0.97)	21 fewer per 1,000 (from 37 fewer to 4 fewer)	Moderate	IMPORTANT
Adverse events - Menopausal symptoms - 5 years follow-up - Sleep disturbances - any grade												
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	serious[b]	none	1456/3221 (45.2%)	1458/3225 (45.2%)	RR 1.00 (0.95 to 1.05)	0 fewer per 1,000 (from 23 fewer to 23 more)	Moderate	IMPORTANT
Adverse events - Menopausal symptoms - 5 years follow-up - Sleep disturbances - grade 2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (HOBOE)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	2/362 (0.6%)	4/351 (1.1%)	RR 0.48 (0.09 to 2.63)	6 fewer per 1,000 (from 10 fewer to 19 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 5 years follow-up Sleep disturbance - grades 3 to 5												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	89/2318 (3.8%)	100/2325 (4.3%)	RR 0.89 (0.67 to 1.18)	5 fewer per 1,000 (from 14 fewer to 8 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 8 years follow-up (any grade) - Sleep disturbance - any grade												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	1375/2317 (59.3%)	1383/2326 (59.5%)	RR 1.00 (0.95 to 1.05)	0 fewer per 1,000 (from 30 fewer to 30 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 8 years follow-up (grades 3 or more) - Insomnia - grades 3 or 4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	89/2317 (3.8%)	105/2326 (4.5%)	RR 0.85 (0.65 to 1.12)	7 fewer per 1,000 (from 16 fewer to 5 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 5 years follow-up (any grade or grade 2) - Fatigue - any grade - Random-effects model (I2 84%)												
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	1620/3221 (50.3%)	1624/3225 (50.4%)	RR 1.08 (0.85 to 1.37)	40 more per 1,000 (from 76 fewer to 186 more)	Very low	IMPORTANT
Adverse events - Menopausal symptoms: Fatigue - 5 years follow-up - grade 2												
1 (HOBOE)	randomised trials	not serious	serious[c]	not serious	not serious	none	2/362 (0.6%)	12/351 (3.4%)	RR 0.16 (0.04 to 0.72)	29 fewer per 1,000 (from 33 fewer to 10 fewer)	Moderate	IMPORTANT
Adverse events - Menopausal symptoms - 5 years follow-up (grades 3 or more) - Fatigue - grades 3 to 4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	73/2318 (3.1%)	67/2325 (2.9%)	RR 1.09 (0.79 to 1.51)	3 more per 1,000 (from 6 fewer to 15 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 8 years follow-up (any grade) - Fatigue - any grade												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	1450/2317 (62.6%)	1496/2326 (64.3%)	RR 0.97 (0.93 to 1.02)	19 fewer per 1,000 (from 45 fewer to 13 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 8 years follow-up (grades 3 or more) - Fatigue - grades 3 or 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	75/2317 (3.2%)	70/2326 (3.0%)	RR 1.08 (0.78 to 1.48)	2 more per 1,000 (from 7 fewer to 14 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 5 years follow-up (any grade or grade 2) - Weight gain - grade 2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (HOBOE)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	3/362 (0.8%)	6/351 (1.7%)	RR 0.48 (0.12 to 1.92)	9 fewer per 1,000 (from 15 fewer to 16 more)	Low	IMPORTANT
Adverse events - Menopausal symptoms - 5 years follow-up (grades 3 or more) - Weight gain - grade 3												
1 (HOBOE)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	1/362 (0.3%)	0/351 (0.0%)	RR 2.91 (0.12 to 71.17)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. I2 was >60%, outcome was downgraded two levels

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. Data was only available from one study, outcome was downgraded one level

Table 90 GRADE table for hypercholesterolemia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Hypercholesterolemia - 5 years follow-up (grade 2) - Hypercholesterolemia - grade 2												
1 (HOBOE)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	7/362 (1.9%)	2/351 (0.6%)	RR 3.39 (0.71 to 16.22)	14 more per 1,000 (from 2 fewer to 87 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. Data was only available from one study, outcome was downgraded one level

Table 91 GRADE table for glucose intolerance

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Glucose intolerance - 5 years follow-up (any grade) - Glucose intolerance - any grade												
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	54/2318 (2.3%)	54/2325 (2.3%)	RR 1.00 (0.69 to 1.46)	0 fewer per 1,000 (from 7 fewer to 11 more)	Low	IMPORTANT
Adverse events - Glucose intolerance - 5 years follow-up (grades 3 or more) - Glucose intolerance - grades 3 to 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	11/2318 (0.5%)	15/2325 (0.6%)	RR 0.74 (0.34 to 1.60)	2 fewer per 1,000 (from 4 fewer to 4 more)	Low	IMPORTANT
Adverse events - Glucose intolerance - 5 years follow-up (any grade) - Hyperglycaemia - grade 2												
1 (HOBOE)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	2/362 (0.6%)	2/351 (0.6%)	RR 0.97 (0.14 to 6.85)	0 fewer per 1,000 (from 5 fewer to 33 more)	Low	IMPORTANT
Adverse events - Glucose intolerance - 5 years follow-up (grades 3 or more) - Hyperglycaemia - grade 3												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
1 (HOBOE)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	0/362 (0.0%)	2/351 (0.6%)	RR 0.19 (0.01 to 4.03)	5 fewer per 1,000 (from 6 fewer to 17 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. Data was only available from one study, outcome was downgraded one level

Table 92 GRADE table for neurocognitive adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Neurocognitive - 5 years follow-up - depression (any grade) - Depression - any grade												
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	serious[a]	none	1211/3221 (37.6%)	1209/3225 (37.5%)	RR 1.00 (0.95 to 1.06)	0 fewer per 1,000 (from 19 fewer to 22 more)	Moderate	IMPORTANT
Adverse events - Neurocognitive - 5 years follow-up - depression (any grade) - Depression - grade 2												
1 (HOBOE)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	9/362 (2.5%)	4/351 (1.1%)	RR 2.18 (0.68 to 7.02)	13 more per 1,000 (from 4 fewer to 69 more)	Low	IMPORTANT
Adverse events - Neurocognitive - 5 years follow-up - depression (grades 3 or more) - Depression - grades 3 to 4												
3 (HOBOE, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	serious[a]	none	87/2680 (3.2%)	104/2676 (3.9%)	RR 0.84 (0.64 to 1.11)	6 fewer per 1,000 (from 14 fewer to 4 more)	Moderate	IMPORTANT
Adverse events - Neurocognitive - 8 years follow-up - depression (any grade) - Depression - any grade												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	1197/2317 (51.7%)	1195/2326 (51.4%)	RR 1.01 (0.95 to 1.06)	5 more per 1,000 (from 26 fewer to 31 more)	Low	IMPORTANT
Adverse events - Neurocognitive - 8 years follow-up - depression (grades 3 or more) - Depression - grades 3 or 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	95/2317 (4.1%)	108/2326 (4.6%)	RR 0.88 (0.67 to 1.16)	6 fewer per 1,000 (from 15 fewer to 7 more)	Low	IMPORTANT
Adverse events - Neurocognitive - 8 years follow-up - memory impairment (any grade) - Memory impairment - grade not reported												
1 (ABCSG-12)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	6/903 (0.7%)	0/900 (0.0%)	RR 12.96 (0.73 to 229.66)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. Data was only available from one study, outcome was downgraded one level

Table 93 GRADE table for psychosexual adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Psychosexual - 5 years follow-up (any grade) - Decreased libido - any grade												
2 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	1042/2318 (45.0%)	950/2325 (40.9%)	RR 1.10 (1.03 to 1.18)	41 more per 1,000 (from 12 more to 74 more)	Moderate	IMPORTANT
Adverse events - Psychosexual - 5 years follow-up (any grade) - Dyspareunia - any grade												
3 (HOBOE, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	not serious	none	708/2680 (26.4%)	602/2676 (22.5%)	RR 1.18 (1.08 to 1.29)	40 more per 1,000 (from 18 more to 65 more)	High	IMPORTANT
Adverse events - Psychosexual - 5 years follow-up (grades 3 or more) - Dyspareunia - grades 3 to 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	53/2318 (2.3%)	32/2325 (1.4%)	RR 1.66 (1.08 to 2.57)	9 more per 1,000 (from 1 more to 22 more)	Moderate	IMPORTANT
Adverse events - Psychosexual - 8 years follow-up (any grade) - Decreased libido - any grade												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	1056/2317 (45.6%)	981/2326 (42.2%)	RR 1.08 (1.01 to 1.15)	34 more per 1,000 (from 4 more to 63 more)	Moderate	IMPORTANT
Adverse events - Psychosexual - 8 years follow-up (any grade) - Dyspareunia - any grade												
2 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	733/2317 (31.6%)	636/2326 (27.3%)	RR 1.16 (1.06 to 1.27)	44 more per 1,000 (from 16 more to 74 more)	Moderate	IMPORTANT
Adverse events - Psychosexual - 8 years follow-up (grades 3 or more) - Dyspareunia - grades 3 or 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[a]	not serious	not serious	none	56/2317 (2.4%)	35/2326 (1.5%)	RR 1.61 (1.06 to 2.44)	9 more per 1,000 (from 1 more to 22 more)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, outcome was downgraded one level

Table 94 GRADE table for musculoskeletal adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Musculoskeletal - 5 years follow-up - Fractures - any grade												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	158/2318 (6.8%)	120/2325 (5.2%)	RR 1.32 (1.05 to 1.66)	17 more per 1,000 (from 3 more to 34 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - 5 years follow-up (grades 3 or more) - Fractures - grades 3 to 4												
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	serious[b]	none	42/3221 (1.3%)	30/3225 (0.9%)	RR 1.40 (0.88 to 2.23)	4 more per 1,000 (from 1 fewer to 11 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - 8 years follow-up (any grade) - Fracture - any grade												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	179/2317 (7.7%)	140/2326 (6.0%)	RR 1.28 (1.04 to 1.59)	17 more per 1,000 (from 2 more to 36 more)	Low	IMPORTANT
Adverse events - Musculoskeletal - 8 years follow-up (grades 3 or more) - Fracture - grade 3 or 4												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	serious[b]	none	51/3220 (1.6%)	35/3226 (1.1%)	RR 1.46 (0.95 to 2.24)	5 more per 1,000 (from 1 fewer to 13 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - 5 years follow-up (any grade) - Random-effects model - Osteoporosis - any grade												
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	921/3221 (28.6%)	636/3225 (19.7%)	RR 0.93 (0.33 to 2.60)	14 fewer per 1,000 (from 132 fewer to 316 more)	Very low	IMPORTANT
Adverse events - Musculoskeletal - 5 years follow-up (grades 3 or more) - Osteoporosis - grades 3 to 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	10/2318 (0.4%)	6/2325 (0.3%)	RR 1.67 (0.61 to 4.59)	2 more per 1,000 (from 1 fewer to 9 more)	Low	IMPORTANT
Adverse events - Musculoskeletal - 8 years follow-up (any grade) - Osteoporosis - any grade												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	not serious	none	977/2317 (42.2%)	648/2326 (27.9%)	RR 1.51 (1.40 to 1.64)	142 more per 1,000 (from 111 more to 178 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - 8 years follow-up (grades 3 or more) - Osteoporosis - grades 3 or 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[c]	not serious	serious[b]	none	10/2317 (0.4%)	7/2326 (0.3%)	RR 1.43 (0.55 to 3.76)	1 more per 1,000 (from 1 fewer to 8 more)	Low	IMPORTANT
Adverse events - Musculoskeletal - 5 years follow-up (any grade) - Random-effects model - Arthralgia - any grade												
1 (ABCSG-12)	randomised trials	not serious	serious[c]	not serious	not serious	none	641/903 (71.0%)	383/900 (42.6%)	RR 1.67 (1.53 to 1.82)	285 more per 1,000 (from 226 more to 349 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - 5 years follow-up (any grade) - Random-effects model - Arthralgia - grade 2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (HOBOE)	randomised trials	not serious	serious[c]	not serious	not serious	none	106/362 (29.3%)	51/351 (14.5%)	RR 2.02 (1.49 to 2.72)	148 more per 1,000 (from 71 more to 250 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - 5 years follow-up (grades 3 or more) - Arthralgia - grade 3												
1 (HOBOE)	randomised trials	not serious	serious[c]	not serious	not serious	none	12/362 (3.3%)	1/351 (0.3%)	RR 11.64 (1.52 to 89.01)	30 more per 1,000 (from 1 more to 251 more)	Moderate	IMPORTANT
Adverse events - Musculoskeletal - 8 years follow-up (any grade) - Arthralgia - any grade												
1 (ABCSG-12)	randomised trials	not serious	serious[c]	not serious	not serious	none	611/903 (67.7%)	359/900 (39.9%)	RR 1.70 (1.55 to 1.86)	279 more per 1,000 (from 219 more to 343 more)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. I2 was >60%, outcome was downgraded two levels

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

c. Data was only available from one study, outcome was downgraded one level

Table 95 GRADE table for cardiovascular adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OFS combined with an AI**	**OFS combined with tamoxifen**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse events - Cardiovascular - 5 years follow-up - deep vein thrombosis or embolism (grades 3 or more) - Deep vein thrombosis or embolism - grades 3 to 4												
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	not serious	none	19/3221 (0.6%)	51/3225 (1.6%)	RR 0.38 (0.23 to 0.64)	10 fewer per 1,000 (from 12 fewer to 6 fewer)	High	IMPORTANT
Adverse events - Cardiovascular - 8 years follow-up - deep vein thrombosis (grades 3 or more) - Deep vein thrombosis - grade 3 or 4												
3 (ABCSG-12, SOFT and TEXT)	randomised trials	not serious	not serious	not serious	not serious	none	20/3220 (0.6%)	53/3226 (1.6%)	RR 0.38 (0.23 to 0.64)	10 fewer per 1,000 (from 13 fewer to 6 fewer)	High	IMPORTANT
Adverse events - Cardiovascular - 5 years follow-up - cardiac ischaemia or infarction (grades 3 or more) - Cardiac ischaemia or infarction - grades 3 to 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	7/2318 (0.3%)	3/2325 (0.1%)	RR 2.34 (0.61 to 9.04)	2 more per 1,000 (from 1 fewer to 10 more)	Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OFS combined with an AI	OFS combined with tamoxifen	Relative (95% CI)	Absolute (95% CI)		
Adverse events - Cardiovascular - 8 years follow-up - cardiac ischaemia or infarction (grades 3 or more) - Cardiac ischaemia or infarction - grade 3 or 4												
2 (SOFT and TEXT)	randomised trials	not serious	serious[b]	not serious	serious[a]	none	7/2317 (0.3%)	6/2326 (0.3%)	RR 1.17 (0.39 to 3.48)	0 fewer per 1,000 (from 2 fewer to 6 more)	Low	IMPORTANT

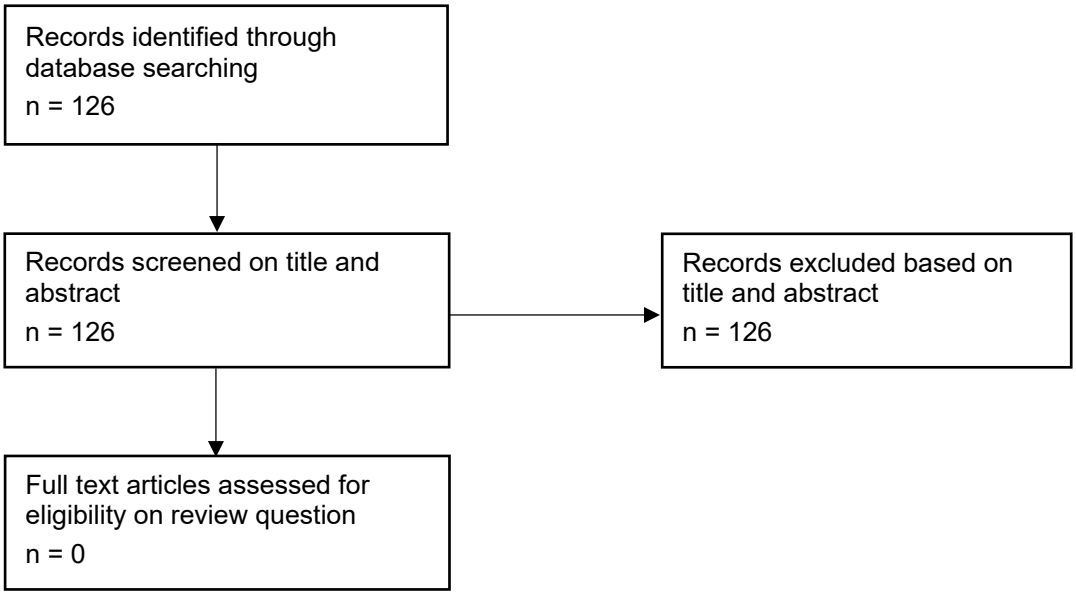
CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level

b. Data was only available from one study, outcome was downgraded one level

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was identified for this review.

Appendix I – Health economic model

No original economic modelling was conducted for this review.

1 Appendix J – Excluded studies

2 Effectiveness studies

Study	Reason for exclusion
Andrahennadi, S., Sami, A., Manna, M. et al. (2021) Current landscape of targeted therapy in hormone receptor-positive and her2-negative breast cancer. Current Oncology 28(3): 1803-1822	- Systematic review used as source of primary studies
Early Breast Cancer Trialists Collaborative Group (2022) Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. The Lancet. Oncology 23(3): 382-392	- Systematic review used as source of primary studies
Azim, Hamdy A, Shohdy, Kyrillus S, Kaldas, David F et al. (2020) Adjuvant ovarian function suppression and tamoxifen in premenopausal breast cancer patients: A meta-analysis. Current problems in cancer 44(6): 100592	- Systematic review used as source of primary studies
Bae, Soong June, Kim, Hee Jeong, Kim, Hyun-Ah et al. (2024) Breast density reduction as a predictor for prognosis in premenopausal women with estrogen receptor-positive breast cancer: an exploratory analysis of the updated ASTRRA study. International journal of surgery (London, England) 110(2): 934-942	- Secondary publication of an included study that does not provide any additional relevant information *Reports survival outcomes by breast density reduction*
Bellet, Meritxell, Gray, Kathryn P, Francis, Prudence A et al. (2016) Twelve-Month Estrogen Levels in Premenopausal Women With Hormone Receptor-Positive Breast Cancer Receiving Adjuvant Triptorelin Plus Exemestane or Tamoxifen in the Suppression of Ovarian Function Trial (SOFT): The SOFT-EST Substudy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34(14): 1584-93	- Secondary publication of an included study that does not provide any additional relevant information *Reports oestrogen levels*
Berglund, G, Nystedt, M, Bolund, C et al. (2001) Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: a prospective randomized study.	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason for exclusion
Journal of clinical oncology : official journal of the American Society of Clinical Oncology 19(11): 2788-96	*Participants were eligible irrespective of their hormone receptor status; there was no data on how many participants were ER positive*
Bernhard, Jurg, Luo, Weixiu, Ribi, Karin et al. (2015) Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials. The Lancet. Oncology 16(7): 848-58	- Data not reported in an extractable format *Mean change and 95% confidence intervals reported only in graphical form*
Buijs, Ciska, de Vries, Elisabeth G E, Mourits, Marian J E et al. (2008) The influence of endocrine treatments for breast cancer on health-related quality of life. Cancer treatment reviews 34(7): 640-55	- Systematic review used as source of primary studies
Chlebowski, Rowan T; Pan, Kathy; Col, Nananda F (2017) Ovarian suppression in combination endocrine adjuvant therapy in premenopausal women with early breast cancer. Breast cancer research and treatment 161(2): 185-190	- Systematic review used as source of primary studies
Dellapasqua, S., Colleoni, M., Gelber, R.D. et al. (2005) Adjuvant endocrine therapy for premenopausal women with early breast cancer. Journal of Clinical Oncology 23(8): 1736-1750	- Comparator in study does not match that specified in protocol *Review with comparisons not listed in our review protocol*
Dowsett, M., Cuzick, J., Ingle, J. et al. (2010) Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. Journal of Clinical Oncology 28(3): 509-518	- Study does not contain a relevant intervention *Ovarian function suppression was not included*
Freedman, O C, Fletcher, G G, Gandhi, S et al. (2015) Adjuvant endocrine therapy for early breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline. Current oncology (Toronto, Ont.) 22(suppl1): 95-s113	- Review article but not a systematic review
Glassman, D., Hignett, S., Rehman, S. et al. (2017) Adjuvant endocrine therapy for hormone-positive breast cancer, focusing on ovarian suppression and extended	- Systematic review used as source of primary studies

Study	Reason for exclusion
treatment: An update. Anticancer Research 37(10): 5329-5341	
Gnant, M., Mlineritsch, B., Schippinger, W. et al. (2009) Endocrine therapy plus zoledronic acid in premenopausal breast cancer. Obstetrical and Gynecological Survey 64(6): 391-393	- Duplicate reference *Obstetrical & Gynaecological Survey presents summaries of clinically relevant research*
Gnant, Michael F X, Mlineritsch, Brigitte, Luschin-Ebengreuth, Gero et al. (2007) Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 25(7): 820-8	- Secondary publication of an included study that does not provide any additional relevant information *Osteoporosis reported at 3 years (Gnant et al. 2008 reported osteoporosis at 5 years)*
Gnant, Michael, Mlineritsch, Brigitte, Schippinger, Walter et al. (2009) Endocrine therapy plus zoledronic acid in premenopausal breast cancer. The New England journal of medicine 360(7): 679-91	- Secondary publication of an included study that does not provide any additional relevant information
Goel, Shom, Sharma, Rohini, Hamilton, Anne et al. (2009) LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. The Cochrane database of systematic reviews: cd004562	- Systematic review used as source of primary studies *Previous version of the Cochrane systematic review by Bui et al. (2020)*
Jiang, M, Chen, W, Hu, Y et al. (2021) Adjuvant ovarian suppression for premenopausal hormone receptor-positive breast cancer: A network meta-analysis. Medicine 100(33): e26949	- Systematic review used as source of primary studies
Johansson, Annelie, Dar, Huma, van 't Veer, Laura J et al. (2022) Twenty-Year Benefit From Adjuvant Goserelin and Tamoxifen in Premenopausal Patients With Breast Cancer in a Controlled Randomized Clinical Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 40(35): 4071-4082	- Study does not contain a relevant outcome *Distant recurrence-free survival*
Kim, Hee J, Noh, Woo C, Nam, Seok J et al. (2021) Five-year changes in ovarian function restoration in premenopausal patients with breast cancer taking tamoxifen	- Study does not contain a relevant outcome *Ovarian function*

Study	Reason for exclusion
after chemotherapy: An ASTRRA study report. European journal of cancer (Oxford, England : 1990) 151: 190-200	
Kim, Hyun-Ah, Ahn, Sei Hyun, Nam, Seok Jin et al. (2016) The role of the addition of ovarian suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or regain menstruation after chemotherapy (ASTRRA): study protocol for a randomized controlled trial and progress. BMC cancer 16: 319	- Protocol
Lee, SJ, Cha, CD, Hong, H et al. (2024) Adverse effects of tamoxifen treatment on bone mineral density in premenopausal patients with breast cancer: a systematic review and meta-analysis. Breast cancer (Tokyo, Japan) 31(4): 717-725	- Systematic review used as source of primary studies
Li, Jian-Wei, Liu, Guang-Yu, Ji, Ya-Jie et al. (2019) Switching to anastrozole plus goserelin vs continued tamoxifen for adjuvant therapy of premenopausal early-stage breast cancer: preliminary results from a randomized trial. Cancer management and research 11: 299-307	- Study does not contain a relevant intervention *Intervention: tamoxifen for 2 to 3 years followed by a switch to aromatase inhibitor (anastrozole) combined with ovarian function suppression (goserelin) for 2 to 3 years*
Li, Jun-Jie and Shao, Zhi-Min (2016) Endocrine therapy as adjuvant or neoadjuvant therapy for breast cancer: selecting the best agents, the timing and duration of treatment. Chinese clinical oncology 5(3): 40	- Systematic review used as source of primary studies
Li, Tianfu, Shan, Zhen, Shi, Yawei et al. (2022) Sequential versus concurrent adjuvant chemo-endocrine therapy for HR+ early breast cancer: a systematic review and Bayesian network meta-analysis. Translational breast cancer research : a journal focusing on translational research in breast cancer 3: 8	- Systematic review used as source of primary studies
Masuda, Norikazu, Sagara, Yasuaki, Kinoshita, Takayuki et al. (2012) Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a	- Study does not contain a relevant intervention *Neoadjuvant setting*

Study	Reason for exclusion
double-blind, randomised phase 3 trial. The Lancet. Oncology 13(4): 345-52	
Meng, Jiajia, Wang, Xiaolan, Guan, Yufu et al. (2020) Aromatase inhibitors plus ovarian function suppression versus tamoxifen plus ovarian function suppression for premenopausal women with early stage breast cancer: a systematic review and meta-analysis. Annals of palliative medicine 9(4): 2294-2302	- Systematic review used as source of primary studies
Nuzzo, F, Gallo, C, Lastoria, S et al. (2012) Bone effect of adjuvant tamoxifen, letrozole or letrozole plus zoledronic acid in early-stage breast cancer: the randomized phase 3 HOBOE study. Annals of oncology : official journal of the European Society for Medical Oncology 23(8): 2027-2033	- Secondary publication of an included study that does not provide any additional relevant information *Reports change of lumbar spine T-score and plasma levels of oestradiol*
Nystedt, M, Berglund, G, Bolund, C et al. (2000) Randomized trial of adjuvant tamoxifen and/or goserelin in premenopausal breast cancer--self-rated physiological effects and symptoms. Acta oncologica (Stockholm, Sweden) 39(8): 959-68	- Secondary publication of an included study that does not provide any additional relevant information *Reports adverse events for all participants without data for participants with ER positive breast cancer*
Nystedt, Marianne, Berglund, Gunilla, Bolund, Christina et al. (2003) Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 21(9): 1836-44	- Secondary publication of an included study that does not provide any additional relevant information
Pagani, Olivia, Francis, Prudence A, Fleming, Gini F et al. (2020) Absolute Improvements in Freedom From Distant Recurrence to Tailor Adjuvant Endocrine Therapies for Premenopausal Women: Results From TEXT and SOFT. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 38(12): 1293-1303	- Study does not contain a relevant outcome *Freedom from distance recurrence*
Pasha, SA, Pasha, AG, Raanaee, M et al. (2020) The role of gnrh analogues in 36-month disease-free survival in non-menopausal patients with hormone receptor-positive breast cancer. Journal of	- Data not reported in an extractable format *Unclear if data was disease-free survival or specific events within the outcome of disease-free survival*

Study	Reason for exclusion
babol university of medical sciences 22(1): 290-297	
Perrone, F, De Laurentiis, M, de Placido, S et al. (2018) The HOBOE-2 multicenter randomized phase III trial in premenopausal patients with hormone-receptor positive early breast cancer comparing triptorelin plus either tamoxifen or letrozole or letrozole + zoledronic acid. Annals of oncology : official journal of the european society for medical oncology 29: viii704	- Conference abstract
Phillips, Kelly-Anne, Regan, Meredith M, Ribi, Karin et al. (2016) Adjuvant ovarian function suppression and cognitive function in women with breast cancer. British journal of cancer 114(9): 956-64	- Secondary publication of an included study that does not provide any additional relevant information *Reports cognitive function pooling data from tamoxifen combined with OFS and an aromatase inhibitor combined with OFS*
Regan, Meredith M, Pagani, Olivia, Fleming, Gini F et al. (2013) Adjuvant treatment of premenopausal women with endocrine-responsive early breast cancer: design of the TEXT and SOFT trials. Breast (Edinburgh, Scotland) 22(6): 1094-100	- Secondary publication of an included study that does not provide any additional relevant information *Reports original designs of TEXT and SOFT and the adaptations to overcome challenges*
Regan, MM, Francis, PA, Pagani, O et al. (2016) Absolute benefit of adjuvant endocrine therapies for premenopausal women with hormone receptor-positive, Human epidermal growth factor receptor 2-Negative early breast cancer: TEXT and SOFT Trials. Journal of clinical oncology 34(19): 2221-2231	- Study does not contain a relevant outcome *Breast cancer-free interval*
Rossi, Emanuela, Morabito, Alessandro, De Maio, Ermelinda et al. (2008) Endocrine effects of adjuvant letrozole + triptorelin compared with tamoxifen + triptorelin in premenopausal patients with early breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26(2): 264-70	- Secondary publication of an included study that does not provide any additional relevant information *Reports hormone levels*
Rutqvist, L E (1994) Randomized adjuvant breast cancer trials in Sweden. Cancer 74(3suppl): 1156-9	- Review article but not a systematic review
Saha, P., Regan, M.M., Pagani, O. et al. (2017) Treatment efficacy, adherence, and	- Data not reported in an extractable format

Study	Reason for exclusion
quality of life among women younger than 35 years in the international breast cancer study group TEXT and SOFT adjuvant endocrine therapy trials. Journal of Clinical Oncology 35(27): 3113-3122	*Mean change and 95% confidence intervals reported only in graphical form*
Salvo, E.M., Ramirez, A.O., Cueto, J. et al. (2021) Risk of recurrence among patients with HR-positive, HER2-negative, early breast cancer receiving adjuvant endocrine therapy: A systematic review and meta-analysis. Breast 57: 5-17	- Systematic review used as source of primary studies
Sverrisdottir, A, Fornander, T, Jacobsson, H et al. (2004) Bone mineral density among premenopausal women with early breast cancer in a randomized trial of adjuvant endocrine therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 22(18): 3694-9	- Study does not contain a relevant outcome *Total body bone density*
Sverrisdottir, A, Nystedt, M, Johansson, H et al. (2009) Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: results from a randomized trial. Breast cancer research and treatment 117(3): 561-7	- Study does not contain a relevant outcome *fertility preservation*
Sverrisdottir, Asgerdur, Johansson, Hemming, Johansson, Ulla et al. (2011) Interaction between goserelin and tamoxifen in a prospective randomised clinical trial of adjuvant endocrine therapy in premenopausal breast cancer. Breast cancer research and treatment 128(3): 755-63	- Comparator in study does not match that specified in protocol *Comparator is 'no endocrine therapy', tamoxifen was only a controlling factor*
Uslu, A, Zengel, B, Akpinar, G et al. (2014) The outcome effect of double-hormonal therapy in premenopausal breast cancer patients with high nodal-status: Result of a prospective randomized trial. Indian journal of cancer 51(4): 582-6	- All participants received chemotherapy
Wells, UM, Moritz, S, Riley, DL et al. (1997) Preliminary report: the CRC adjuvant breast cancer trial for patients under the age of fifty. Breast (Edinburgh, Scotland) 6(4): 255	- Conference abstract
Yan, Shunchao, Li, Kai, Jiao, Xin et al. (2015) Tamoxifen with ovarian function suppression versus tamoxifen alone as an	- Systematic review used as source of primary studies

Study	Reason for exclusion
adjuvant treatment for premenopausal breast cancer: a meta-analysis of published randomized controlled trials. OncoTargets and therapy 8: 1433-41	
Yang, H, Zong, X, Yu, Y et al. (2013) Combined effects of goserelin and tamoxifen on estradiol level, breast density, and endometrial thickness in premenopausal and perimenopausal women with early-stage hormone receptor-positive breast cancer: a randomised controlled clinical trial. British journal of cancer 109(3): 582-8	- Study does not contain a relevant outcome *Breast density, endometrial thickness, oestradiol, and lipidaemia*
Yoshida, T, Takahashi, O, Suzuki, Y et al. (2023) The effectiveness of controlled ovarian stimulation with tamoxifen for patients with estrogen-sensitive breast cancer: A systematic review and meta-analysis. Reproductive medicine and biology 22(1): e12543	- Comparator in study does not match that specified in protocol *Tamoxifen compared to aromatase inhibitor*
Zhang, P, Li, C-Z, Jiao, G-M et al. (2017) Effects of ovarian ablation or suppression in premenopausal breast cancer: A meta-analysis of randomized controlled trials. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 43(7): 1161-1172	- Systematic review used as source of primary studies

Economic studies

None: as no studies were sifted at full text.

Appendix K– Research recommendations – full details

K1.1 Research recommendation

What is the real-world evidence on the long-term adverse events and effects on quality of life of using ovarian function suppression in combination with either tamoxifen or an aromatase inhibitor in premenopausal people with ER positive invasive breast cancer?

K1.1.1 Why this is important

OFS combined with tamoxifen or OFS combined with an AI was reported in the included studies with the longest follow up being 12 years. The committee highlighted that the long-term consequences of these treatments and effects on quality of life due to inducing the menopause prematurely are unclear. They agreed that data from real-world evidence could provide clarity on these long-term consequences from studies with follow-up 15 years and longer.

K1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the long-term consequences and effects on quality of life of the prematurely induced menopause using ovarian function suppression in combination with either tamoxifen or an aromatase inhibitor in premenopausal people with ER positive invasive breast cancer. A greater understanding on this will help to provide the best intervention to premenopausal people with ER positive invasive breast cancer.
Relevance to NICE guidance	The evidence in this review was from studies with up to 12 years follow-up looking at the clinical and cost effectiveness of using ovarian function suppression in combination with either tamoxifen or an aromatase inhibitor in premenopausal people with ER positive invasive breast cancer. New evidence with a follow-up of at least 15 years could be used to update recommendations.
Relevance to the NHS	New evidence with at least 15 years follow-up in premenopausal people with ER positive invasive breast cancer using ovarian function suppression in combination with either tamoxifen or an aromatase inhibitor could help clinicians to discuss the long-term consequences and effects on quality of life of the prematurely induced menopause using these treatments.
National priorities	No specific national priorities
Current evidence base	No long data was identified in this review.
Equality considerations	A list of health inequalities issues were identified during the development of recommendations on ovarian function suppression and listed in the equality and health inequalities assessment.

K1.1.3 Modified PICO table

Population	**Inclusion:**

	• Adults (18 and over) with invasive ER positive breast cancer and female reproductive organs who are premenopausal or perimenopausal. People with female reproductive organs covers women, trans men and non-binary people who currently have ovaries. The invasive breast cancer is of any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0). **Exclusion:** Adults (18 and over) with: • invasive ER positive breast cancer and female reproductive organs who are postmenopausal • invasive breast cancer that is not ER positive. • metastatic breast cancer (covered by CG81 currently). • newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Paget's disease of the breast with no invasive component.
Intervention	• Ovarian function suppression combined with an aromatase inhibitor* or combined with tamoxifen) Ovarian function suppression using: ○ Luteinising-hormone releasing hormone (LHRH) agonists of interest: buserelin, goserelin, leuprorelin, nafarelin, and triptorelin. These have to be used for at least 12 months. ○ Oophorectomy (bilateral) *Aromatase inhibitors of interest: anastrozole, exemestane and letrozole.
Comparator	• Ovarian function suppression combined with an aromatase inhibitor compared to ovarian function suppression combined with tamoxifen • Tamoxifen without ovarian function suppression compared to ovarian function suppression combined with an aromatase inhibitor • Tamoxifen without ovarian function suppression compared to ovarian function suppression combined with tamoxifen
Outcome	• Overall survival • Disease-free survival • Local and/or locoregional recurrence • New contralateral disease • Long-term adverse events/ toxicity • Quality of life • Adherence to or completion of treatment
Study design	Real world evidence (cohort study)
Timeframe	Long-term (15 or more years follow-up)
Additional information	Cost-effectiveness analysis should be done if evidence is available

1

Appendix L – Methods

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the PROSPERO register of systematic reviews.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2024 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were contacted for missing data when time and resources allowed (when this occurred, this was noted in the evidence review and relevant data was included).

Incorporating published evidence syntheses

If published evidence syntheses were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were considered for use as the primary source of data, rather than extracting information from primary studies. Syntheses considered for inclusion in this way were quality assessed to assess their suitability using the appropriate checklist, as outlined in Table 96. Note that this quality assessment was solely used to assess the quality of the synthesis in order to decide whether it could be used as a source of data, as outlined in Table 97, not the quality of evidence contained within it, which was assessed in the usual way as outlined in the section on 'Appraising the quality of evidence'.

Table 96 Checklists for published evidence syntheses

Type of synthesis	Checklist for quality appraisal
Systematic review of quantitative evidence	ROBIS

Each published evidence synthesis was classified into one of the following three groups:

High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.

Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.

Low quality – It is possible that relevant and important studies have been missed by the review.

Each published evidence synthesis was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

Fully applicable – The identified review fully covers the review protocol in the guideline.

Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).

Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

The way that a published evidence synthesis was used in the evidence review depended on its quality and applicability, as defined in Table 97. When published evidence syntheses were used as a source of primary data, data from these evidence syntheses were quality assessed and presented in GRADE tables in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were checked to ensure none of the data had been double counted through this process.

Table 97 Criteria for using published evidence syntheses as a source of data

Quality	Applicability	Use of published evidence synthesis
High	Fully applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted.
High	Partially applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted. For other sections not covered by the evidence synthesis, searches were undertaken as normal.

Quality	Applicability	Use of published evidence synthesis
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the evidence synthesis, searches were undertaken as normal.

Methods of combining evidence

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. When there were 2 treatment alternatives, pairwise meta-analysis was used to compare interventions.

Pairwise meta-analysis

Pairwise meta-analyses were performed in Cochrane Review Manager (web version). A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Random-effects models were fitted when significant between-study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken. For all other syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as $I2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses were less heterogeneous (with $I2 < 50\%$) the results from these subgroups were reported using fixed-effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

RCTs were quality assessed using the Cochrane Risk of Bias Tool 2. Risk of bias for single studies were conducted once for objective outcomes, once for subjective outcomes, and once for adverse events. Where there is a published approach to overall risk of bias judgement this should be used. Where there is no published approach developers should use their judgement and include a statement of the rationale for the overall judgement included in EPPI and evidence table. Evidence on each outcome for each individual study was classified into one of the following groups:

Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.

Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.

High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Where systematic reviews were used as a source of evidence for RCTs but they do not use the Cochrane Risk of Bias Tool 1 for risk of bias, the judgements were taken from that review and converted to Cochrane risk of bias Tool 2 judgements so that all RCTs were assessed in the same way. Descriptions of the approach taken are written in the methods specific to the review.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.

Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.

Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a clinical decision threshold to be defined to act as a non-inferiority margin.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. Clinical decision threshold that were used in the guideline are given in Table 98 and also reported in the relevant evidence reviews.

Table 98 Identified Clinical decision thresholds

Outcome	Clinical decision threshold	Source
Quality of life FACT-G total	3 to 7 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life FACT-B total	7 to 8 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life TOI (trial outcome index) of FACT-B	5 to 6 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life BCS of FACT-B	2 to 3 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life WHOQOL-100	1 point	Den Oudsten, B.L., Zijlstra, W.P. & De Vries, J. The minimal clinical important difference in the World Health Organization Quality of Life instrument—100. Support Care Cancer 21, 1295–1301 (2013). https://doi.org/10.1007/s00520-012-1664-8

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 99. These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 99 Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than <50% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than >50% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 50% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	Not serious: If less than <50% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than >50% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than >50% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. Not serious: If the I^2 was less than <40%, the outcome was not downgraded. Serious: If the I^2 was between 41% and 60%, the outcome was downgraded one level or if data on the outcome was only available from one study. Very serious: If the I^2 was greater than >60%, the outcome was downgraded two levels.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was

GRADE criteria	Reasons for downgrading quality
	not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

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Appendix M – List of adverse events of interest

Type of adverse event
Genitourinary
Vaginal dryness/ atrophy pooled
Repeated urinary tract infections
Incontinence
Menopausal symptoms
Vasomotor symptoms (= hot flushes, sweats, night sweats, vasodilation pooled)
Sleep disturbances, somnolence and insomnia pooled
Fatigue/ tiredness
Weight gain
Hypercholesterolemia
Glucose intolerance (including hyperglycaemia and hypoglycaemia as pooled terms)
Neurocognitive
Cognitive function (cognitive disorder, memory and concentration problems pooled)
Depression
Anxiety
Psychosexual
Sexual function (e.g., Lower libido, pain on intercourse = dyspareunia pooled)
Musculoskeletal
Fracture
Osteoporosis
Arthralgia =bone and muscle pain pooled with arthropathy (achy joints)
Cardiovascular (Grade 3 or 4 only)
DVT, PE (VTE umbrella term, thrombosis, embolism- pooled)
Stroke
Cardiac ischaemia
Other cancers (pooled with footnotes): not graded, reported as incidence [With Tmx-endometrial cancer/ pituitary tumour rare benign tumour with goserelin]