National Institute for Health and Care Excellence

Final

Early and locally advanced breast cancer: diagnosis and management

[J] Evidence reviews for neoadjuvant treatment

NICE guideline NG101

Evidence reviews

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Final

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Neoadjuvant treatment

This evidence report contains information on 4 reviews relating to neoadjuvant treatment.

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Review question 10.1 What is the effectiveness of neoadjuvant chemotherapy?

Introduction

The standard treatment for breast cancer remains surgical resection followed by adjuvant therapies, where indicated such as chemotherapy, endocrine therapy, biological therapies and radiotherapy. However, neoadjuvant therapies (given before surgery), may result in tumour shrinkage facilitating breast conserving surgery or smaller resections.

Trials of neoadjuvant chemotherapy have generally enrolled participants with early/operable breast carcinoma and studies have confirmed the equivalence of this approach to more traditional adjuvant chemotherapy. From these early studies it was apparent that oestrogen receptor (ER) status, grade and histological subtype were predictive of response. However defining the strength of such associations was hindered by the various histological definitions used to categorise tumour response. Furthermore the heterogeneity of chemotherapy effect seen in neoadjuvant trials was at odds with the large Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analysis which show similar proportional risk reductions for the different intrinsic subtypes of breast cancer.

More recent analyses have confirmed that response to neoadjuvant treatment provides important prognostic information, with pathological complete response to neoadjuvant chemotherapy correlating with disease-free survival. This association is strongest for triple negative breast cancer and human-epidermal growth factor receptor 2 (HER2) enriched subtypes. Identification of predictive markers associated with response to primary chemotherapy will help select those patients who have most to gain from this approach.

The aim of this review is to determine if neoadjuvant chemotherapy (with or without biological therapy) is clinically and cost effective, and to determine which subgroups should be offered this treatment.

PICO table

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults (18 or over) with invasive breast cancer (M0) who are planned to have surgery
Intervention	Anthracycline-containing neoadjuvant chemotherapy regimens ± biological therapy
Comparison	No neoadjuvant chemotherapy ± biological therapy
Outcomes	**Critical** • Local recurrence • Disease-free survival **Important** • Pathological complete response • Breast-conservation rate • Overall survival • Response rates

M0, no distant metastases

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Eleven randomised controlled trials (number of participants, N=4588) were included in the review (Bordeaux 1991, Deo 2003, European Cooperative Trial in Operable Breast Cancer [ECTO] 2005, European Organisation for Research and Treatment of Cancer [EORTC] 10902, Institut Curie 1991, Institut Curie 1994, Japan 1998, National Surgical Adjuvant Breast and Bowel Project [NSABP] B-18, Royal Marsden 1998, USA 2003 and Zhao 2016). Evidence from these trials is summarised in the clinical GRADE evidence profile in Table 3.

See also the study selection flow chart in appendix C, forest plots in Appendix E and study evidence tables in appendix D.

This review is an update of a topic in the previous guideline CG80 (NICE 2009) - although the current review is limited to anthracycline-containing regimes. The recommendations made in CG80 were based on evidence from a Cochrane review including 14 RCTs (van der Hage, 2007). The current review includes the 9 trials from that Cochrane review which used anthracycline-containing regimes (Bordeaux 1991, ECTO 2005, EORTC 10902, Institut Curie 1991, Institut Curie 1994, Japan 1998, NSABP B-18, Royal Marsden 1998 and USA 2003), but updated with longer follow-up where available, as well as 1 trial excluded from the Cochrane review (Deo 2003) and a new trial published since (Zhao 2016).

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies. The patient characteristics (where reported) were comparable between trials except for Deo 2003 which was limited to patients with tumour stage 4b. Although human epidermal growth factor receptor 2 (HER2) status and triple negative disease were specified as subgroups of interest in the review protocol these were not reported in any of the trials.

The treatment received in each trial is summarised in Table 3. Six of the trials compared neoadjuvant with adjuvant chemotherapy (Bordeaux 1991, ECTO 2005, EORTC 10902, Institut Curie 1994, NSABP B-18 and USA 2003). The remaining 5 trials (Institut Curie 1991, Japan 1998, Royal Marsden and Zhao 2016) compared neoadjuvant + adjuvant chemotherapy with adjuvant chemotherapy.

Locoregional treatment was typically breast conserving therapy or mastectomy, however in three French trials (Bordeaux 1991, Institut Curie 1991 and Institut Curie 1994) some patients were treated with RT alone if they responded to neoadjuvant therapy. In 2 of the trials (Deo 2003 and Japan 1998) surgery was always mastectomy. In Bordeaux 1991 patients in the no-neoadjuvant arm all received mastectomy.

Table 2: Summary of included studies

Study	Trial ID	Additional inclusion/exclusion criteria	Interventions/comparison
Mauriac 1999	Bordeaux 1991	Inclusion criteria • Adult women with operable breast cancer with or without nodal involvement (i.e. T2>3cm or T3 N0-1 M0) • Oral informed consent. Exclusion criteria • Women with T4, N2-3 tumours; • Metastatic disease.	• Neoadjuvant arm: EVM + MTV then RT± BCT or mastectomy . Adjuvant treatments: no adjuvant chemo and no adjuvant RT or TAM • Comparison arm: no neoadjuvant chemo then mastectomy . Adjuvant treatments: ±EVM + MTV and no adjuvant RT or TAM
Deo 2003	Deo 2003	Inclusion criteria • Untreated female patients with bidimensionally palpable and measurable primary operable breast cancer (i.e. T4b, N0-2, M0; AJCC TNM, 6th ed.) • Diagnosis by fine-needle aspiration cytology • Adequate organ function (leukocyte count>4000 mm3; haemoglobin>9.5 g/dL; aspartate aminotransferase and alanine aminotransferase<100 IU/ml; serum creatinine<1.2 mg/dl; creatinine clearance>60 ml/min) • Informed consent. Exclusion criteria • ECOG performance stats III or IV • Inoperable locally advanced disease (extensive oedema of breast and arm, or axillary lymph nodes fixed to underlying structures) • Inflammatory BC • Evidence of metastases • Pregnancy • Patients with left ventricular ejection fraction<50% if radionuclide scan clinically indicated.	• Neoadjuvant arm: CEF then mastectomy . Adjuvant treatments: CEF and RT • Comparison arm: no neoadjuvant chemo then mastectomy . Adjuvant treatments: CEF and RT
Gianni 2005	ECTO 2005	Inclusion criteria • Female patient at participating institution; • >18 years-old; • Untreated primary operable breast tumour >2 cm (T2-3, N0-1, M0); • known hormone receptor status and tumour grade; • Karnofsky PS>70; • adequate bone marrow, renal and liver function; • normal blood pressure and cardiac function (inc. left ventricular ejection fraction); • written informed consent Exclusion criteria	• Neoadjuvant arm: AT-CMF then BCT or mastectomy. Adjuvant treatments: no adjuvant chemo and ±RT, TAM • Comparison arm: no neoadjuvant chemo then BCT or mastectomy. Adjuvant treatments: AT-CMF and ±RT, TAM

Study	Trial ID	Additional inclusion/exclusion criteria	Interventions/comparison
		• Locally advanced or bilateral breast carcinoma; • prior anticancer treatment; inadequate bone marrow reserve; • abnormal renal and liver function tests; • history of cardiac disease; • pregnancy or lactating; • active infection; • history of other invasive malignancy; • psychiatric disorder preventing informed consent.	
Van Nes 2009	EORTC 10902	Inclusion criteria • Female patient at participating institution • Primary operable breast cancer (T1c-T4b), N0-1, M0) • Core-needle biopsy for either diagnosis of T1c tumours or doubt/suspicion of carcinoma in-situ after fine-needle aspiration • Informed consent. Exclusion criteria • Age 70 years or more • Bilateral BC • Previous BC treatment • Presence distant metastases • Pregnancy or lactation at diagnosis • Previous/current other malignancies except adequately-treated skin or cervix uteri basal or squamous carcinoma • Active cardiac disease • WHO performance status >2; • Severe haematologic, renal or hepatic abnormalities.	• Neoadjuvant arm: FEC then BCT or mastectomy . Adjuvant treatments: no adjuvant chemo and ±RT, TAM • Comparison arm: no neoadjuvant chemo then BCT or mastectomy . Adjuvant treatments: FEC and ±RT, TAM
Scholl 1991[1]	Institut Curie 1991	Inclusion criteria • Women only • Operable breast cancer (T2-3, N0-1b, M0) • Age <65 yrs Exclusion criteria • Prior cancer • Serious concomitant illness	• Neoadjuvant arm: FAC then RT± BCT or mastectomy . Adjuvant treatments: FAC or AMVT and no adjuvant RT or TAM • Comparison arm: no neoadjuvant chemo then RT± BCT or mastectomy . Adjuvant treatments: FAC and no adjuvant RT or TAM
Broet 1999	Institut Curie 1994	Inclusion criteria • Women only • Premenopausal • M0 operable breast tumour • Largest tumour 3-7 cm • Axillary lymph nodes not clinically involved or involved but not adherent	• Neoadjuvant arm: FAC then RT± BCT or mastectomy . Adjuvant treatments: no adjuvant chemo and no adjuvant RT or TAM • Comparison arm: no neoadjuvant chemo then

Study	Trial ID	Additional inclusion/exclusion criteria	Interventions/comparison
		• No prior cancer • No serious concomitant illness. Exclusion criteria • Bilateral, inflammatory or locally advanced BC	RT± BCT or mastectomy . Adjuvant treatments: FAC and no adjuvant RT or TAM
Enomoto 1998[1]	Japan 1998	Inclusion criteria • Women only • Histologically confirmed breast cancer • Stage II with tumour size >4 cm or stage III.	• Neoadjuvant arm: EC then mastectomy . Adjuvant treatments: EC and TAM • Comparison arm: no neoadjuvant chemo then mastectomy . Adjuvant treatments: EC and TAM
Fisher 1998	NSABP B-18	Inclusion criteria • Female patient at participating NSABP institution; • Primary, palpable, operable breast cancer; (i.e. T1-3, N0-1, M0); • Diagnosis of BC using fine-needle aspiration or core biopsy; • Written informed consent. Exclusion criteria • Diagnosis of BC using open (incisional or excision) biopsy.	• Neoadjuvant arm: AC then BCT or mastectomy . Adjuvant treatments: no adjuvant chemo and ±RT, TAM • Comparison arm: no neoadjuvant chemo then BCT or mastectomy . Adjuvant treatments: AC and ±RT, TAM
Makris 1998[1]	Royal Marsden 1998	Inclusion criteria • Women only • Histologically confirmed primary, operable breast cancer (T1-4, N0-1, M0) Exclusion criteria • Premenopausal women who wanted to consider further pregnancy • Clinical evidence of myocardial dysfunction.	• Neoadjuvant arm: (M)MM + TAM then BCT or mastectomy ±RT . Adjuvant treatments: MM(M) or FEC and no adjuvant RT or TAM • Comparison arm: no neoadjuvant chemo then BCT or mastectomy ±RT . Adjuvant treatments: (M)MM and TAM
Danforth 2003	USA 2003	Inclusion criteria • Women only • Untreated Stage II BC (i.e. T1-2, N0-1 [AJCC 1989] • Histologically-confirmed invasive breast cancer of epithelial origin (patients with bilateral BC eligible only if at least one invasive tumour and most advanced cancer at least clinical stage II • Leukocyte count >4000/mm3; platelet count >100,000/mm3 • Liver chemistries < 1.5 times normal upper limits; • Creatinine <1.7 mL/min and/or creatinine clearance >45 mL/min • Absence of chronic cardiac or pulmonary disease • Written informed consent.	• Neoadjuvant arm: FLAC + G(M)-CSF then BCT or mastectomy . Adjuvant treatments: no adjuvant chemo and RT, TAM • Comparison arm: - then BCT or mastectomy . Adjuvant treatments: FLAC + G(M)-CSF and RT, TAM

Study	Trial ID	Additional inclusion/exclusion criteria	Interventions/comparison
		Exclusion criteria • Patients with excisional biopsy followed by subsequent treatment; or with history of malignant neoplasms except for those who have had (i) (pre-1997) curatively-treated basal cell carcinoma of skin, (ii) (pre-1997) surgically-excised carcinoma of cervix in situ, or (iii) (post-1997 only) curative therapy of non-breast malignancy and no evidence of recurrence after 10 or more years; • Pregnancy	
Zhao 2016	Zhao 2016	Inclusion criteria • Female patient at Xuzhou Cancer Hospital, Jiangsu, China • Advanced invasive breast cancer by clinical examination • Written, informed consent.	• Neoadjuvant arm: CAF then BCT or mastectomy . Adjuvant treatments: CAF and no adjuvant RT or TAM • Comparison arm: - then BCT or mastectomy . Adjuvant treatments: CAF and no adjuvant RT or TAM

[1] *Study characteristics and results for the Makris 1998, Enomoto 1998 and Scholl 1991 trials were extracted from the van der Hage, 2007 systematic review.*
±, with or without; AC, doxorubicin, cyclophosphamide; AT-CMF, doxorubicin, paclitaxel, cyclophosphamide, methotrexate, fluorouracil; BC, breast cancer; BCT breast conserving therapy; CAF, cyclophosphamide, doxorubicin, fluorouracil ; CEF, cyclophosphamide, epirubicin, fluorouracil; EC, epirubicin, cyclophosphamide; ECTO, European Cooperative Trial in Operable Breast Cancer; EORTC, European Organisation for Research and Treatment of Cancer; EVM , epirubicin, vincristine, methotrexate; FAC, fluorouracil, doxorubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; FLAC , fluorouracil, leucovorin, doxorubicin, cyclophosphamide; G(M)-CSF, granulocyte(-macrophage) colony-stimulating factor; MMM, mitomycin, methotrexate, mitoxantrone; NSABP, National Surgical Adjuvant Breast and Bowel Project; PS, performance status; RT, radiotherapy; TAM, tamoxifen; WHO, World Health Organization

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question is presented in Table 3 and the summary of predictive factors is presented in Table 4.

Table 3: Summary clinical evidence profile: Comparison 1. Anthracycline-containing neoadjuvant chemotherapy versus no neoadjuvant chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No neoadjuvant chemotherapy	Neoadjuvant chemotherapy			
Local recurrence Follow-up: 8 to 16 years	91 per 1000	105 per 1000 (89 to 125)	HR 1.16 (0.98 to 1.38)	4275 (6 studies[1])	High

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No neoadjuvant chemotherapy	Neoadjuvant chemotherapy			
Locoregional recurrence free survival (LRFS) Follow-up: 5 to 16 years	8yr LRFS 88%[8]	8yr LRFS 86% (84% to 89%)[8]	HR 1.15 (0.96 to 1.37)	4414 (7 studies[1])	High
Disease-free survival (DFS) Follow-up: 2 to 16 years	8yr DFS 55%[7]	8yr DFS 55% (50% to 58%)[7]	HR 0.99 (0.9 to 1.08)	4240 (9 studies)	High
Breast-conservation therapy rate Follow-up: post-op	495 per 1000	643 per 1000 (529 to 776)	RR 1.3 (1.07 to 1.57)	3859 (6 studies)	Low[3]
Pathologic complete response after neoadjuvant chemotherapy Follow-up: post-op	Not applicable	Pathologic complete response ranged from 4% to 23%	Not estimable	1765 (4 studies)	Low[4]
Overall survival (OS) Follow-up: 2 to 16 years	8yr OS 72%[7]	8yr OS 73% (70% to 75%)[7]	HR 0.97 (0.87 to 1.08)	4240 (9 studies)	High
Objective response after neoadjuvant chemotherapy Follow-up: post-op	Not applicable	Objective response ranged from 11% to 83%	Not estimable	2173 (7 studies)	Low[4]
Any post-operative complications Follow-up: post-op	16 per 1000	11 per 1000 (4 to 35)	RR 0.71 (0.23 to 2.20)	751 (2 studies)	Low[5,6]
Cardiotoxicity Follow-up: during or post-chemotherapy	101 per 1000	75 per 1000 (54 to 105)	RR 0.74 (0.53 to 1.04)	1600 (2 studies)	Low[2,6]
Leucopaenia, neutropaenia or infection Follow-up: during or post-chemotherapy	138 per 1000	95 per 1000 (77 to 116)	RR 0.69 (0.56 to 0.84)	2799 (4 studies)	High
Nausea or vomiting Follow-up: during or post-chemotherapy	158 per 1000	171 per 1000 (130 to 223)	RR 1.08 (0.82 to 1.41)	1088 (2 studies)	Low[2,6]
Alopecia Follow-up: during or post-chemotherapy	538 per 1000	528 per 1000 (490 to 565)	RR 0.98 (0.91 to 1.05)	2561 (3 studies)	High

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; LRFS, local recurrence free survival; OS, overall survival; RR, risk ratio

[1] Excluding mastectomy only trials – due to serious heterogeneity

[2] 95% confidence interval crosses boundary for no effect (1) and one minimally important difference (0.8 and 1.25) based on GRADE default values

[3] Very serious heterogeneity, I-squared = 91%; random effects model used - no pre-specified subgroups accounted for heterogeneity.

[4] *Study design was observational for this outcome – as data only came from the neoadjuvant arm*
[5] *95% confidence interval crosses boundary for no effect (1) and both minimally important differences (0.8 and 1.25) based on GRADE default values*
[6] *< 300 events*
[7] *Using 8 year survival rates from the no-neoadjuvant chemotherapy arm of NSABP B-18*
[8] *Using 8 year survival rates from the no-neoadjuvant chemotherapy arm of EORTC 10902*

Table 4: Predictive factors for response to anthracycline-containing neoadjuvant chemotherapy

Trial	Outcome	Predictive factors examined	Independent predictors of response on multivariate analysis. RR or OR (95% CI)
Bordeaux 1991	Clinical response > 50%	Tumour size ≤40 mm, SBR grade 3, SBR grade 1, IHC-ER < 10%, IHC-PR < 10%, DCC-ER < 10 fmol/mg protein-1, DCC-PR < 15 fmol/mg protein-1 , MIB1 > 40%, pS2 < 3%, p53 < 0%, c-erb-B2 < 1 and glutathione-S-transferase pi(GST4)	Tumour size ≤40 mm : RR 3.88 (1.6 – 9.3) IHC-ER < 10% (ER negative): RR 3.29 (1.4 – 7.6) MIB1 > 40%:RR 4.12 (1.4 – 11.5)
Deo 2003	Clinical response	Tumour size, nodal status and age	None
ECTO 2005	Clinically complete response	Age, clinical tumour size, clinical nodal status, ER and progesterone receptor status, and tumour grade	ER negative: OR 2.1 (1.36 – 3.23)
	Pathologic response	Age, clinical tumour size, clinical nodal status, ER and progesterone receptor status, and tumour grade	ER negative: OR 5.77 (3.49 – 9.52)

CI confidence interval; DCC dextran-coated charcoal; ECTO, European Cooperative Trial in Operable Breast Cancer; ER oestrogen receptor; IHC immunohistochemistry ; MIB1 mindbomb E3 ubiquitin protein ligase 1 ; OR odds ratio; PR progesterone receptor; RR risk ratio; SBR Scarff-Bloom-Richardson;

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Anthracycline-containing neoadjuvant chemotherapy versus no neoadjuvant chemotherapy

Critical outcomes

Local recurrence

- There is high quality evidence from 6 RCTs (N=4275) that local recurrence may be more likely in people treated with anthracycline-containing neoadjuvant chemotherapy compared to those receiving no neoadjuvant chemotherapy but there is uncertainty about the estimate.

Disease-free survival

- There is high quality evidence from 9 RCTs (N=4240) which indicates no clinically important difference in disease-free survival between people treated with anthracycline-containing neoadjuvant chemotherapy and those receiving no neoadjuvant chemotherapy.
- Treatment effects in terms of local recurrence or disease-free survival were not reported according to subgroups of surgery versus no surgery, tumour grade, HER-2 status, ER status, triple negative or histological subtype.

Important outcomes

Pathological complete response

- No evidence was found for this outcome.

Breast conservation rate

- There is low quality evidence from 6 RCTs (N=3859) that people treated with anthracycline-containing neoadjuvant chemotherapy are more likely to receive breast conserving surgery than those not treated with neoadjuvant chemotherapy.

Overall survival

- There is high quality evidence from 9 RCTs (N=4240) of no clinically important difference in overall survival between people treated with anthracycline-containing neoadjuvant chemotherapy and those receiving no neoadjuvant chemotherapy.

Response rates

- There is low quality observational evidence from the neoadjuvant arms of 7 RCTs (N=2173) that the objective response rate following anthracycline-containing neoadjuvant chemotherapy ranges from 11% to 83%.
- There is low quality observational evidence from the neoadjuvant arms of 7 RCTs (N=2173) that the pathological complete response rate following anthracycline-containing neoadjuvant chemotherapy ranges from 4% to 23%.
- ER negative status was an independent predictive factor for clinical response to anthracycline containing neoadjuvant chemotherapy in two studies that conducted multivariate analysis. Tumour grade was not an independent predictive factor in these studies. HER-2 status, triple negative or histological subtype were not considered in the multivariate analyses.
- ER negative status was an independent predictive factor for pathologic response to anthracycline-containing neoadjuvant chemotherapy in one study that conducted multivariate analysis. Tumour grade was not an independent predictive factor in this study. HER-2 status, triple negative or histological subtype were not considered in the multivariate analysis.

Treatment related adverse events

- There is low quality evidence from 2 RCTs (N=1600) of no clinically important difference in the rates of cardiotoxicity in people treated with anthracycline-containing neoadjuvant chemotherapy and people receiving no neoadjuvant chemotherapy.
- There is high quality evidence from 4 RCTs (N=2799) of a clinically important reduction in the rates of leucopaenia, neutropaenia and infection in people treated with anthracycline-containing neoadjuvant chemotherapy compared with people receiving no neoadjuvant chemotherapy.
- There is low quality evidence from 2 RCTs (N=1088) of no clinically important difference in the rates of nausea or vomiting in people treated with anthracycline-containing neoadjuvant chemotherapy and people receiving no neoadjuvant chemotherapy.

- There is high quality evidence from 3 RCTs (N=2561) of no clinically important difference in the rates of alopecia in people treated with anthracycline-containing neoadjuvant chemotherapy and people receiving no neoadjuvant chemotherapy.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The critical outcomes were local recurrence and disease-free survival. This was because an important reason for offering for neoadjuvant chemotherapy is to enable breast conserving therapy instead of mastectomy, but this potentially carries an increased risk of disease recurrence. Important outcomes were breast conservation rate, overall survival, pathological and clinical response to chemotherapy as these are indicators of who is likely to benefit from the treatment.

The quality of the evidence

The quality of the evidence for breast conservation rate, survival and recurrence outcomes was low to high using GRADE. Although the chemotherapy regimens used in some of the older trials were outdated, these studies compared the timing of chemotherapy (before versus after surgery) rather than different regimens. For this reason these trials were still considered relevant.

Three of the trials specified that locoregional treatment was always mastectomy in one or both of the trial arms. This not in line with current clinical practice and was a source of heterogeneity in the analysis of local recurrence. For this reason the committee used the evidence about locoregional recurrence from the subgroup of trials where any patient could potentially receive breast conserving treatment.There was limited evidence about which patients would gain most benefit from neoadjuvant chemotherapy in the absence of subgroup comparisons according to HER2 status, triple negative disease or histological subtype. Low quality evidence indicated that ER-negative disease would be more likely to respond to neoadjuvant chemotherapy, but the committee agreed that some people with ER-positive disease might also benefit and a weaker recommendation was made for this subgroup.

The committee acknowledged existing NICE technology appraisal guidance (TA424) which recommends neoadjuvant pertuzumab in patients with HER-2 positive breast cancer and the committee agreed it was important that this group was offered neoadjuvant chemotherapy.

Benefits and harms

Neoadjuvant chemotherapy increases breast conservation rates with potentially improved patient satisfaction. There is potentially less chemotherapy related cardiotoxicity, neutropenia and leucopoenia. Neoadjuvant chemotherapy also allows earlier assessment of chemotherapy response which can be used to predict outcome and to select an alternative regimen after surgery if needed.

There may be a small increase in the absolute risk of local recurrence following neoadjuvant chemotherapy, possibly due to increased use of breast conserving therapy. Neoadjuvant chemotherapy often downstages nodal disease before surgery so the planning of adjuvant radiotherapy relies on radiological rather than pathological staging of lymph nodes.

The committee thought that the benefits of neoadjuvant chemotherapy outweighed the small risk of local recurrence and uncertainty in planning adjuvant radiotherapy, given the evidence indicated no associated change in overall or disease-free survival.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee acknowledged there would be more monitoring needed to assess disease response during neoadjuvant chemotherapy; however, the resource impact is unlikely to be large as a number of centres already offer this treatment. Although the treatment pathway is more complex with neoadjuvant chemotherapy, there is a potential cost saving with less reconstructive surgery needed for those able to receive breast conserving therapy.

Other factors the committee took into account

The committee considered making a research recommendation to investigate how the response to neoadjuvant chemotherapy may affect subsequent local therapy. However, it was noted that ongoing and planned studies are investigating the accuracy of post-chemotherapy imaging and tumour bed biopsy as predictors of pathological complete response. Only when these techniques (either individually or in combination) have been rigorously validated, will it be possible to design studies which de-escalate local treatment in women whose tumours show an excellent response to neoadjuvant systemic treatment

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Review question 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

Introduction

The standard treatment for breast cancer remains surgical resection followed by adjuvant therapies, where indicated such as chemotherapy, endocrine therapy, biological therapies and radiotherapy. However, neoadjuvant therapies (given before surgery), may result in tumour shrinkage facilitating breast conserving surgery or smaller resections.

Endocrine therapy is an established therapy for oestrogen receptor (ER) positive invasive breast cancer. Endocrine therapy is traditionally used in the adjuvant setting (following surgery) with the aim of reducing breast cancer recurrence (both locoregional recurrence and distant metastases). Endocrine therapy is commonly given in the form of a daily tablet with a low toxicity, which can safely be given in the community, without additional invasive monitoring.

The aim of this review was to determine if neoadjuvant endocrine therapy is effective in people with early or locally advanced breast cancer, and could be used before surgery to facilitate breast conserving surgery.

PICO table

See Table 5 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 5: Summary of the protocol (PICO table)

Population	Adults (18 or over) with ER-positive / HER2 unknown or HER2-negative invasive breast cancer (M0) who have not yet undergone surgery
Intervention	• Neoadjuvant endocrine therapy
Comparison	• No neoadjuvant endocrine therapy • Neoadjuvant chemotherapy
Outcome	**Critical** • Disease-free survival • Breast conservation rates • Changes in tumour size **Important** • Overall survival • Local recurrence following surgery • HRQoL

ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; M0, no distant metastases; HRQoL, health-related quality of life

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Five articles (N=934) were included in the review (Alba 2012; Marcus 2013; Mustacchi 2003; Palmieri 2014; Semiglazov 2007); 4 randomised controlled trials and 1 retrospective cohort study.

Four trials included in the current evidence review compared neoadjuvant endocrine therapy with neoadjuvant chemotherapy and 1 trial compared neoadjuvant endocrine therapy with no neoadjuvant therapy.

Four studies (Alba 2012; Marcus 2013; Palmieri 2014; Semiglazov 2007) reported data for subgroups of interest: pre-menopausal (number of publications, k=1), post-menopausal (k=4), grade 3 (k=1). One study (Alba 2012) also reported data for grade 1 and grade 2 tumours combined.

The clinical studies included in this evidence review are summarised in Table 6 and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 7 and Table 8).

See also the study selection flow chart in appendix C, forest plots in appendix E and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 6: Summary of included studies

Study	Additional inclusion/exclusion criteria	Interventions/comparison
Alba 2012	• PR+ and cytokeratin 8/18+; tumour >2cm and/or axillary node involvement; ECOG performance status ≤1; normal cardiac, liver and renal function; adequate bone marrow • Exclusion: received treatment for current disease; receiving corticosteroids ER modulators or HRT; inflammatory or bilateral breast cancer; co-morbid uncontrolled systemic disease; cancer within last 10 years (other than skin); child-bearing potential without use of adequate contraception	• Intervention arm (NET): oral exemestane 25 mg daily for 24 weeks. Pre-menopausal patients also received 3.6mg goserelin subcutaneously every 28 days for six cycles. After neoadjuvant treatment patients underwent surgery • Control arm (NACT): epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 both administered intravenously (i.v.) on day 1 every 21 days, for four cycles followed by docetaxel 100 mg/m^2 administered i.v. on day 1 every 21 days for four cycles. Pre-menopausal patients also received 3.6mg goserelin subcutaneously every 28 days for six cycles. After neoadjuvant treatment patients underwent surgery
Marcus 2013	• Post-menopausal women with non-inflammatory ER+ breast cancer • Exclusion: HER2+	• Intervention arm (NET): The delivery, type, dose and duration of NET was determined by the treating medical oncologist. 93% received an aromatase inhibitor and 7% received tamoxifen • Control arm (NACT): The delivery, type, dose and duration of NET was determined by the treating medical oncologist. 51%

Study	Additional inclusion/exclusion criteria	Interventions/comparison
		received both anthracycline and taxane, 38% received anthracycline only
Mustacchi 2003	• Aged ≥70 years • Exclusion: unfit for surgery/unavailable for follow-up; previous/concurrent malignancy (except treated skin cancer or in situ cervical cancer); prior chemotherapy and/or hormone therapy	• Intervention arm (NET): patients received 160 mg loading dose of tamoxifen on day 1, followed by 20 mg daily for 5 years • Control arm (No NET): Surgery (82% radical) followed by tamoxifen 20 mg/day for 5 years
Palmieri 2014	• Post-menopausal women aged ≥70 years; tumour had to be ≥20mm and/or nodal disease ≥20mm • Exclusion: not able to biopsy primary tumour	• Intervention arm (NET): 2.5mg oral letrozole was given once daily for 18-23 weeks (until day before surgery) • Control arm (NACT): FEC100C chemotherapy or FE75C given at 3 weekly intervals for 6 cycles. Patients were switched to docetaxel (100mg/m^2 every 3 weeks for 3 cycles) if disease was stable or progressive
Semiglazov 2007	• Post-menopausal women; ER+ and/or PR+ breast cancer; stage IIA to IIIB; life expectancy ≥6 months; adequate bone marrow, renal and hepatic function • Exclusion: uncontrolled cardiac disease; bilateral or inflammatory breast cancer; concurrent HRT; other malignancies	• Intervention arm (NET): patients were randomised within this arm to receive either 25mg exemestane or 1mg anastrozole daily for 3 months. Surgery was scheduled for 3 months from date patient first received medication • Control arm (NACT): patients received chemotherapy with doxorubicin 60 mg/m^2 and paclitaxel 200 mg/m^2 every 3 weeks for 4 cycles. Surgery was scheduled for 3 months from date patient first received treatment with chemotherapy

ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FEC, fluorouracil, epirubicin, cyclophosphamide; HER2, human epidermal growth factor receptor 2; HRT, hormone replacement therapy; NACT, neoadjuvant chemotherapy; NET, neoadjuvant endocrine therapy; PR, progesterone receptor

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question (neoadjuvant endocrine therapy) are presented in Table 3 and Table 4. The majority of the evidence was low or very low; the main reasons studies were downgraded was because of imprecision due to small number of events of interest and large confidence intervals. There was also some indirect evidence due to the inclusion of people with oestrogen receptor negative (ER-) tumours.

Table 7: Summary clinical evidence profile: Comparison 1. Neoadjuvant endocrine therapy versus no neoadjuvant endocrine therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: No NET	Corresponding risk: NET			
OS (6.7 year follow-up)	6.7yr OS 46%	6.7yr OS 45% (37% to 54%)	HR 1.02 (0.80 to 1.29)	474 (1 study)	Low[1,2]

CI: Confidence interval; ER, oestrogen receptor; HR: Hazard ratio; NET: neoadjuvant endocrine therapy; OS: overall survival
[1] Proportion of patients ER+ unknown - only assessed in 24%
[2] <300 events

Table 8: Summary clinical evidence profile: Comparison 2. Neoadjuvant endocrine therapy versus neoadjuvant chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: NACT	Corresponding risk: NET			
Breast conservation rates - Whole sample	468 per 1000	562 per 1000 (379 to 833)	RR 1.2 (0.81 to 1.78)	95 (1 study)	Low[1]
Breast conservation rates - Post-menopausal	237 per 1000	330 per 1000 (218 to 498)	RR 1.39 (0.92 to 2.1)	239 (1 study)	Very low[1,2]
Changes in tumour size - Clinical response - Whole sample – partial	532 per 1000	415 per 1000 (271 to 638)	RR 0.78 (0.51 to 1.2)	95 (1 study)	Low[3]
Changes in tumour size - Clinical response - Whole sample - complete	128 per 1000	63 per 1000 (17 to 235)	RR 0.49 (0.13 to 1.84)	95 (1 study)	Low[4]
Changes in tumour size - Clinical response - Pre-menopausal	750 per 1000	442 per 1000 (278 to 720)	RR 0.59 (0.37 to 0.96)	51 (1 study)	Moderate[5]
Changes in tumour size - Clinical response - Post-menopausal	565 per 1000	526 per 1000 (305 to 899)	RR 0.93 (0.54 to 1.59)	44 (1 study)	Low[4]
Changes in tumour size - Clinical response - Post-menopausal - partial	550 per 1000	649 per 1000 (462 to 907)	RR 1.18 (0.84 to 1.65)	283 (2 studies)	Very low[1,6]
Changes in tumour size - Clinical response - Post-menopausal - complete	107 per 1000	66 per 1000 (13 to 338)	RR 0.62 (0.12 to 3.15)	283 (2 studies)	Very low[4,6]
Changes in tumour size - Clinical response - Grade 1/2	683 per 1000	499 per 1000 (341 to 731)	RR 0.73 (0.5 to 1.07)	79 (1 study)	Low[4]
Changes in tumour size - Clinical response - Grade 3	500 per 1000	400 per 1000 (135 to 1000)	RR 0.8 (0.27 to 2.41)	16 (1 study)	Low[4]
Changes in tumour size - Radiological response - Post-menopausal - unspecified method partial	455 per 1000	591 per 1000 (332 to 1000)	RR 1.3 (0.73 to 2.31)	44 (1 study)	Low[4]
Changes in tumour size - Radiological response - Post-menopausal - unspecified method complete	91 per 1000	18 per 1000 (1 to 358)	RR 0.2 (0.01 to 3.94)	44 (1 study)	Low[4]
Changes in tumour size - Radiological response - Post-menopausal - ultrasound partial	424 per 1000	373 per 1000 (271 to 508)	RR 0.88 (0.64 to 1.2)	239 (1 study)	Very low[2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: NACT	Corresponding risk: NET			
Changes in tumour size - Radiological response - Post-menopausal - ultrasound complete	42 per 1000	33 per 1000 (9 to 120)	RR 0.78 (0.21 to 2.83)	239 (1 study)	Very low[2,4]
Changes in tumour size - Radiological response - Post-menopausal - mammography partial	559 per 1000	548 per 1000 (436 to 688)	RR 0.98 (0.78 to 1.23)	239 (1 study)	Very low[2,3]
Changes in tumour size - Radiological response - Post-menopausal - mammography complete	68 per 1000	58 per 1000 (22 to 155)	RR 0.85 (0.32 to 2.28)	239 (1 study)	Very low[2,4]
Overall survival (non-RCT) – post menopausal (4 year follow-up)	4yr OS 86%	4yr OS 91% (69% to 98%)	HR 0.61 (0.15 to 2.45)	99 (1 study)	Very low[5,7]

CI: Confidence interval; ER: oestrogen receptor; HR: Hazard ratio; NACT, neoadjuvant chemotherapy; NET: neoadjuvant endocrine therapy; RCT: randomised controlled trials; RR: Risk ratio

[1] 95% confidence interval crosses both no effect (1) and minimally important difference (1.25) based on GRADE default values; <300 events

[2] 14% of sample ER-

[3] 95% confidence interval crosses both no effect (1) and minimally important difference (0.8) based on GRADE default values; <300 events

[4] 95% confidence interval crosses both no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values; <300 events

[5] <300 events

[6] 14% of Semiglazov 2007 sample ER-; this study has 77% of weight in the analysis

[7] Groups not comparable; more advanced T stage, N stage, and Grade in NACT arm. Also higher rates of PR- and adjuvant radiotherapy in NACT arm

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Neoadjuvant endocrine therapy versus no neoadjuvant endocrine therapy

Critical outcomes

Disease-free survival

- No evidence was found for this outcome.

Breast conservation rates

- No evidence was found for this outcome.

Changes in tumour size

- No evidence was found for this outcome.

Important outcomes

Overall survival

- There is low quality evidence from 1 RCT (N=474) that there is no clinically important effect of neoadjuvant endocrine therapy on overall survival at 6.7 year follow-up for people with ER+, HER2-/unknown invasive breast cancer

Local recurrence following surgery

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 2. Neoadjuvant endocrine therapy versus neoadjuvant chemotherapy

Critical outcomes

Disease-free survival

- No evidence was found for this outcome.

Breast conservation rates

- There is low quality evidence from 1 RCT (N=95) that there is no clinically meaningful difference in breast conservation rates following neoadjuvant endocrine therapy or neoadjuvant chemotherapy for mixed populations of people with ER+ / HER2 unknown or HER2- invasive breast cancer
- There is very low quality evidence from 1 RCT (N=239) that neoadjuvant endocrine therapy produces clinically meaningful increases in breast conservation rates compared with neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer. However, this was not statistically significant

Changes in tumour size - partial clinical response

- There is low quality evidence from 1 RCT (N=95) that neoadjuvant endocrine therapy produces clinically meaningful reductions in the number of individuals with a partial clinical response compared with neoadjuvant chemotherapy for mixed populations of people with ER+ / HER2 unknown or HER2- invasive breast cancer. However, this was not statistically significant.
- There is very low quality evidence from 2 RCTs (N=283) that there is no clinically meaningful difference in partial clinical response rates following neoadjuvant endocrine therapy or neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer.

Changes in tumour size - complete clinical response

- There is low quality evidence from 1 RCT (N=95) that neoadjuvant endocrine therapy produces clinically meaningful reductions in the number of individuals with a complete clinical response compared with neoadjuvant chemotherapy for mixed populations of people with ER+ / HER2 unknown or HER2- invasive breast cancer. However, this was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=51) that neoadjuvant endocrine therapy produces clinically meaningful reductions in the number of individuals with a clinical response compared with neoadjuvant chemotherapy for pre-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer

- There is low quality evidence from 1 RCT (N=44) that there is no clinically meaningful difference in clinical response rates following neoadjuvant endocrine therapy or neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer.
- There is very low quality evidence from 2 RCTs (N=283) that neoadjuvant endocrine therapy produces clinically meaningful reductions in the number of individuals with a complete clinical response compared with neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer. However, this was not statistically significant.
- There is low quality evidence from 1 RCT (N=79) that neoadjuvant endocrine therapy produces clinically meaningful reductions in the number of individuals with a complete clinical response compared with neoadjuvant chemotherapy for people with grade 1 or grade 2, ER+ / HER2 unknown or HER2- invasive breast cancer. However, this was not statistically significant.
- There is low quality evidence from 1 RCT (N=16) that neoadjuvant endocrine therapy produces clinically meaningful reductions in the number of individuals with a complete clinical response compared with neoadjuvant chemotherapy for people with grade 3, ER+ / HER2 unknown or HER2- invasive breast cancer. However, this was not statistically significant.

Changes in tumour size - radiological response

- There is low quality evidence from 1 RCT (N=44) that neoadjuvant endocrine therapy produces clinically meaningful increases in the number of individuals with a partial radiological response (unspecified method) compared with neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer. However, this was not statistically significant.
- There is low quality evidence from 1 RCT (N=44) that neoadjuvant endocrine therapy produces clinically meaningful reductions in the number of individuals with a complete radiological response (unspecified method) compared with neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer. However, this was not statistically significant.
- There is very low quality evidence from 1 RCT (N=239) that there is no clinically meaningful difference in partial radiological response rates as measured by ultrasound following neoadjuvant endocrine therapy or neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=239) that neoadjuvant endocrine therapy produces clinically meaningful reductions in the number of individuals with complete radiological response rates as measured by ultrasound compared with neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer. However, this was not statistically significant.
- There is very low quality evidence from 1 RCT (N=239) that there is no clinically meaningful difference in partial radiological response rates as measured by mammography following neoadjuvant endocrine therapy or neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=239) that there is no clinically meaningful difference in complete radiological response rates as measured by mammography following neoadjuvant endocrine therapy or neoadjuvant chemotherapy for post-menopausal women with ER+ / HER2 unknown or HER2- invasive breast cancer.

Important outcomes

Overall survival

- There is very low quality evidence from 1 RCT (N=474) that there is no clinically important difference in overall survival at 4 year follow-up following neoadjuvant endocrine therapy or neoadjuvant chemotherapy for post-menopausal women with ER+, HER2-/unknown invasive breast cancer

Local recurrence following surgery

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As the primary aim of review was to determine the effectiveness of endocrine therapy in the neoadjuvant setting, the committee identified breast-conservation rates and changes in tumour size as critical outcomes, as well as disease-free survival.

Breast-conservation rates and changes in tumour size where prioritised ahead of overall survival and local recurrence following surgery (which were identified as important outcomes) as the primary goal of neoadjuvant therapy is to downsize tumours. This facilitates breast-conserving surgery in patients who would otherwise require mastectomy as the clinical tumour size is too large relative to breast size for conservation. However, it is important to include overall survival as an outcome to evaluate whether neoadjuvant endocrine therapy is detrimental to survival as there is a risk of disease progression if therapy is ineffective.

Health-related quality of life was also identified by the committee as an important outcome as this may be impacted by treatment-related morbidities and conservation rates. Breast conservation rates are a critical outcome for service users as mastectomy can have a significant impact on quality of life.

No evidence was available for disease-free survival, local recurrence following surgery or health-related quality of life.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. For breast conservation rates and changes in tumour size the quality was very low to low, mainly due to uncertainty around the estimate due to the small number of events of interest and wide confidence intervals, but also due to some indirect evidence due to inclusion of ER- individuals in some studies. However, there was moderate quality evidence in pre-menopausal women that fewer individuals have a clinical response following neoadjuvant endocrine therapy than following neoadjuvant chemotherapy.

Overall survival evidence was very low to low quality because of issues with imprecision due to small number of events and also because this evidence was based on 1 RCT with an indirect population and 1 retrospective cohort study with significant differences in baseline characteristics between arms.

The low quality of the evidence affected the strength of the recommendations, with only a weak recommendation being made. Also, the recommendation was specific to post-

menopausal women as there was very limited evidence for pre-menopausal women and that which was available suggested that chemotherapy may be superior to endocrine therapy in this group.

The recommendation to discuss the benefits and harms of alternative treatments with the patient so they can make an informed decision, was made based on the Committee's knowledge and experience. However, the Committee agreed that due to the uncertainty in this area and the balance of benefits with the very different side-effect profiles and patient acceptability of endocrine therapy compared to chemotherapy, this recommendation was essential to ensure best clinical practice.

Benefits and harms

Although there was little difference in the effectiveness of chemotherapy and endocrine therapy in post-menopausal women, the recommendation to consider neoadjuvant endocrine therapy as an option to facilitate breast conservation provides a greater number of treatment options for patients. Also, the committee were aware that endocrine therapy has fewer and less severe side effects compared with chemotherapy, is typically given as tablets than can be quickly self-administered at home whereas chemotherapy is delivered in hospital, and is therefore less disruptive and likely to be preferred by patients.

The potential harms from these recommendations include the potential for disease progression during treatment if endocrine therapy is ineffective. Endocrine therapy also does have some side-effects but the committee discussed the fact that all eligible patients would receive endocrine therapy following surgery, even if they had not received it before surgery. Therefore the endocrine therapy-related side-effects will just be experienced earlier in a patient's treatment course.

The committee balanced the harms and benefits by confirming that in post-menopausal women neoadjuvant endocrine therapy and neoadjuvant chemotherapy were equally effective but that the treatment-related comorbidity was much less with the endocrine therapy. The committee noted that the clinical evidence had not suggested any detrimental effect on overall survival but active monitoring should be continued to mitigate risk of disease progression.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee thought there could be cost increases associated with the use of endocrine therapy (if neoadjuvant treatment is not currently being used). However, the cost of endocrine therapy is relatively small and in comparison to neoadjuvant chemotherapy, it is much cheaper. Endocrine therapy drug costs are less costly than chemotherapy and also do not require hospital time or medical staff to administer the treatment. In comparison to chemotherapy, there are also fewer and less severe adverse events with endocrine therapy, which would further reduce costs.

The use of endocrine therapy may also lead to a reduction in surgery costs as it may allow for more patients to have breast conserving surgery rather than a mastectomy. However, the committee noted that there is the potential for cost increases if endocrine therapy is ineffective and disease progresses (however this risk should be reduced through active monitoring).

On balance, the committee thought the recommendations would lead to cost savings if more people opt for endocrine therapy rather than chemotherapy. However, the committee noted that the use of endocrine therapy is already standard practice in most centres in the UK and so no significant changes in resources are anticipated.

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Review question 10.3 What are the indications for postmastectomy radiotherapy following neoadjuvant systemic therapy?

Introduction

Randomised controlled trials (RCTs) have shown that achieving a pathologically complete response (pCR) within the breast or sterilising involved axillary nodes is associated with excellent long term outcomes including reduced local recurrence rates, whereas cohort analysis (Mamounas 2012) of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials of neoadjuvant chemotherapy (B-18 and B-27) have shown a high risk of local recurrence in people with any degree of residual nodal involvement. Therefore, this review aims to identify the role of post mastectomy radiotherapy in people who have received neoadjuvant systemic therapies.

PICO table

See Table 9 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 9: Summary of the protocol (PICO table)

Population	Adults (18 or over) with invasive breast cancer (M0) who have undergone neoadjuvant systemic therapy and mastectomy
Intervention	• Radiotherapy to the chest wall • Radiotherapy to the chest wall and regional nodes
Comparison	• No radiotherapy
Outcome	**Critical** • Locoregional recurrence rate • Disease-free survival • Treatment-related morbidity **Important** • Overall survival • HRQoL

M0, no distant metastases; HRQoL, health-related quality of life

For details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Eleven articles (N=13,565) were included in the review (Abdel-Wahab 1998; Garg 2007; Huang 2004; Le Scodan 2012; Liu 2016; McGuire 2007; Meattini 2014; Nagar 2011; Nagar 2015; Rusthoven 2016; Shim 2014), which all report data from retrospective cohort studies.

Four trials report on subgroups of participants from the University of Texas M. D. Anderson Cancer Center and one trial reports data for participants in the National Cancer Database.

All of the trials included in the current evidence review compared postmastectomy radiotherapy to the chest wall and regional nodes following neoadjuvant chemotherapy with no postmastectomy radiotherapy. None of the included studies examined the efficacy of postmastectomy radiotherapy to the chest wall only.

Nine studies (Garg 2007; Huang 2004; Le Scodan 2012; Liu 2016; McGuire 2007; Meattini 2014; Nagar 2011; Rusthoven 2016; Shim 2014) reported data for subgroups of interest in the following categories: 1) clinical T stages cT1, (k=1), cT1/2 (k=1), cT2 (k=3), cT3 (k=4), cT4 (k=3); 2) clinical N stages cN0 (k=3), cN1 (k=3), cN2 (k=3), cN2/3 (k=1), cN3 (k=1);); 3) pathological T stages pT0/Tx/Tis (k=2), pT2 (k=1), pT3 (k=1), pT4 (k=1); and 4) pathological N stages pN0 (k=5), pN1 (k=2), pN2 (k=2), pN2/3 (k=1), pN3 (k=1), A number of studies also reported data for clinical and pathological T and N stages combined: cT1/2pN0 (k=1), cT3cN0 (k=1), cT3pN0 (k=1), cN1pN0 (k=1), cN2/3pN0 (k=1), pT0//TispN0 (k=1), pT1/2pN0 (k=1), pN0cT1/2 (k=1) and pN0cT3/4 (k=1). No studies reported subgroup data based on surgical margin status.

The clinical studies included in this evidence review are summarised in Table 10 and evidence from these are summarised in the clinical GRADE evidence profile below (Table 11). See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 10: Summary of included studies

Study	Additional inclusion/exclusion criteria	Interventions/comparison
Abdel-Wahab 1998	• Clinically palpable T3, T4, N2, and N3 breast cancer	• Intervention arm (RT chest wall + nodes): Neoadjuvant chemotherapy using IV MVAC was given in a 28-day cycle until either complete response (CR) was achieved or the maximum response had been achieved. Participants then underwent modified radical mastectomy and 6 courses of adjuvant MVAC chemotherapy. Postoperative radiation therapy to the chest wall was required 4 to 6 weeks after completing systemic therapy. Radiation to the axilla, supraclavicular region, and chest-wall boost were left to the discretion of the radiation oncologist. • Control arm (No RT): Neoadjuvant chemotherapy using IV MVAC was given in a 28-day cycle until either complete response (CR) was achieved or the maximum response had been achieved. Participants then underwent modified radical mastectomy and 6 courses of adjuvant MVAC chemotherapy.
Garg 2007	• <35 years old with stage II and II breast cancer on protocols for neoadjuvant doxorubicin-based chemotherapy and mastectomy	• Intervention arm (RT to chest wall + nodes): The chest wall was usually treated with medial and lateral tangents using photons designed to include the entire chest wall (median dose

Study	Additional inclusion/exclusion criteria	Interventions/comparison
		50 Gy). A separate supraclavicular anterior photon field was matched at the non-divergent superior border of the tangential fields designed to encompass the undissected Level III axilla and axillary apex (median dose 50 Gy). An electron field was often matched medially to the medial tangential field, with particular care to cover the internal mammary nodal region while respecting critical structures, including the heart and lung (median dose 50 Gy). Finally, the chest wall was typically boosted (median dose 10 Gy) with electrons designed to include the mastectomy scar with an adequate margin. • Control arm (No RT): No further details reported
Huang 2004	• Inclusion criteria not reported - data comes from six prospective trials that investigated the role of doxorubicin-based neoadjuvant chemotherapy for participants with nonmetastatic, noninflammatory breast cancer	• Intervention arm (RT to chest wall + nodes): All participants received doxorubicin as part of a combination neoadjuvant chemotherapy regimen; 15% also received a taxane. All participants were treated with mastectomy; after neoadjuvant chemotherapy and mastectomy 95% received adjuvant chemotherapy; 34% also received tamoxifen. Postoperative radiotherapy included the chest wall and typically draining lymphatics (median dose 50Gy) followed by a chest wall boost (median dose 10Gy). • Control arm: All participants received doxorubicin as part of a combination neoadjuvant chemotherapy regimen; 15% also received a taxane. All participants were treated with mastectomy; after neoadjuvant chemotherapy and mastectomy 95% received adjuvant chemotherapy; 34% also received tamoxifen.
Le Scodan 2012	• Stage II or Stage III breast cancer participants that received had pathologic N0 status (pN0) after neoadjuvant chemotherapy	• Intervention arm (RT to chest wall + nodes): All NAC was anthracycline based; mastectomy included axillary dissection. Post mastectomy radiotherapy targeted the chest wall, supraclavicular lymph nodes, and internal mammary nodes to a total dose of 45–50Gy (daily fractions of 1.8-2.0Gy). PMRT typically used a photon field to treat the supraclavicular fossa/axillary apex, a mixed photon and electron field to treat the internal mammary chains, and an electron field to treat the chest wall. • Control arm (No RT): All NAC was anthracycline based; mastectomy included axillary dissection.
Liu 2016	• Clinically node-positive and stage II-III breast cancer, treated with NAC and mastectomy with pathologically confirmed complete nodal response (ypN0)	• Intervention arm (RT to chest wall + nodes): radiation targets included chest wall and draining lymphatics, with or without a chest wall boost. The median dose of radiation was 50.4Gy. • Control arm (No RT): No details reported

Study	Additional inclusion/exclusion criteria	Interventions/comparison
	• Exclusion: positive or unknown surgical margin; pathological tumour size > 5 cm after NAC; distant metastatic disease; prior malignancy; unknown clinical or pathological tumour/node stage; preoperative or intraoperative radiotherapy	
McGuire 2007	• Women who had achieved a pCR after receiving neoadjuvant chemotherapy who had mastectomy • Exclusion: inflammatory breast cancer	• Intervention arm (RT to chest wall + nodes): 92% received an anthracycline as a component of the neoadjuvant chemotherapy, and 38% received a taxane either pre- or postoperatively. All participants underwent a modified radical mastectomy that included a level I or II axillary dissection. Post mastectomy radiotherapy typically targeted the chest wall and draining lymphatics with 50 Gy in 25 fractions over 5 weeks, followed by a boost to the chest wall consisting of 10 Gy in five fractions over 1 week. The undissected draining lymphatics were typically treated with two separate fields, a photon field targeting the supraclavicular fossa/axillary apex, and an electron field targeting the internal mammary chain and medial chest wall. • Control arm (No RT): 92% received an anthracycline as a component of the neoadjuvant chemotherapy, and 38% received a taxane either pre- or postoperatively. All participants underwent a modified radical mastectomy that included a level I or II axillary dissection.
Meattini 2014	• Exclusion: previous solid tumours; BC recurrences or contralateral tumour	• Intervention arm (RT to chest wall + nodes): 99% received anthracyclines as part of combination neoadjuvant chemotherapy regimen; 41% also received a taxane. All participants received mastectomy. Post mastectomy radiotherapy treatment volumes typically included the chest wall and draining lymphatics, consisting in the supraclavicular (SCV) and infraclavicular (ICV) nodal region (total dose 50Gy; 2Gy daily fractions), with mixed photon and electron beams technique, chosen at physician discretion. • Control arm (no RT): 99% received anthracyclines as part of combination neoadjuvant chemotherapy regimen; 41% also received a taxane.
Nagar 2015	• Clinically staged T1 to T3/N0 to N3 M0 breast cancer	• Intervention arm (RT to chest wall + nodes): All participants received preoperative chemotherapy. Most (93%) participants received anthracycline-based chemotherapy, with approximately 80% of participants receiving a combination of anthracycline and taxane-based chemotherapy. All participants underwent mastectomy. Post mastectomy radiotherapy radiation was delivered to the

Study	Additional inclusion/exclusion criteria	Interventions/comparison
		chest wall and regional lymph nodes (axilla, supraclavicular fossa, and internal mammary lymph nodes). • Control arm (No RT): All participants received preoperative chemotherapy. Most (93%) participants received anthracycline-based chemotherapy, with approximately 80% of participants receiving a combination of anthracycline and taxane-based chemotherapy. All participants underwent mastectomy.
Nagar 2011	• Clinically staged T3N0 tumours	• Intervention arm (RT to chest wall + nodes): All participants received preoperative chemotherapy. The majority received anthracycline-based chemotherapy, with approximately one-third receiving anthracycline and taxane. All participants underwent mastectomy. Post mastectomy radiation was delivered to the chest wall and regional nodal basins (high axilla and supraclavicular fossa, with or without the internal mammary chain). Typically, the lateral chest wall was treated with medial-lateral tangential photon fields, while the medial chest wall and underlying internal mammary chain were treated with an anteroposterior oblique electron field. The axillary apex and supraclavicular fossa were treated with an anteroposterior oblique photon field. • Control arm (No RT): All participants received preoperative chemotherapy. The majority received anthracycline-based chemotherapy, with approximately one-third receiving anthracycline and taxane. All participants underwent mastectomy.
Rusthoven 2016	• cT1–3, cN1, M0 breast cancer	• Intervention arm (RT to chest wall + nodes): All participants received neoadjuvant chemotherapy and mastectomy. No information available about types of chemotherapy received or hormonal therapy. Post mastectomy radiotherapy targeted the chest wall ± regional nodes. • Control arm: All participants received neoadjuvant chemotherapy and mastectomy. No further details reported.
Shim 2014	• Tumour size >5 cm or axillary LN metastasis who achieved pN0 after neoadjuvant chemotherapy • Exclusion: distant metastases; clinically positive supraclavicular or internal mammary lymph nodes; inflammatory or bilateral breast cancer; previous or concurrent malignancy except for thyroid cancer; previous chemotherapy or radiation therapy	• Intervention arm (RT to chest wall + nodes): All participants received preoperative chemotherapy. The most common NAC regimen was a combination of anthracycline and taxane, followed by anthracycline-based and taxane-based chemotherapy. All participants underwent mastectomy and the majority received complete axillary lymph node dissection. Adjuvant chemotherapy was performed in 72% of participants. Post mastectomy radiotherapy delivered 45-50 Gy to the chest wall, supraclavicular lymph

Study	Additional inclusion/exclusion criteria	Interventions/comparison
		nodes, and internal mammary nodes. The chest wall was treated with a photon tangential field or reverse hockey stick (photon-electron field). The supraclavicular fossa was treated with an anteroposterior oblique photon field. • Control arm (No RT): All participants received preoperative chemotherapy. The most common NAC regimen was a combination of anthracycline and taxane, followed by anthracycline-based and taxane-based chemotherapy. All participants underwent mastectomy and the majority received complete axillary lymph node dissection. Adjuvant chemotherapy was performed in 72% of participants.

BC, breast cancer; CR, complete response; Gy; Gray; IV, intravenous; IVC, infraclavicular; LN, lymph node; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; NAC, neoadjuvant chemotherapy; PMRT, postmastectomy radiotherapy; RT, radiotherapy; SVC, supraclavicular

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (postmastectomy radiotherapy after neoadjuvant chemotherapy) is presented in Table 11 The majority of the evidence was low or very low because of the observational nature of the included studies, imprecision due to small number of events and risk of bias due to differences in patient characteristics between study arms. However, large hazard ratios increased the quality of some evidence.

Table 11: Summary clinical evidence profile: Comparison 1. Postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy versus no radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: RT-	Corresponding risk: RT+			
Locoregional recurrence - mixed population (4 to 10 year follow-up)	69% free from LRR at 4 yrs	87% fee from LRR at 4 yrs (81% to 91%)	HR 0.38 (0.26 to 0.56)	1008 (4 studies)	Very low[1,2]
Locoregional recurrence - T stage subgroups - cT2 (5 to 10 year follow-up)	64% free from LRR at 5 yrs	87% free from LRR at 5 yrs (69% to 95%)	HR 0.32 (0.12 to 0.84)	199 (3 studies)	Very low[1,2]
Locoregional recurrence - T stage subgroups - cT3 (5 to 10 year follow-up)	57% free from LRR at 5 yrs	90% free from LRR at 5 yrs (80% to 95%)	HR 0.19 (0.09 to 0.4)	320 (3 studies)	Very low[1,2]
Locoregional recurrence - T stage subgroups - cT4 (5 to 10 year follow-up)	57% free from LRR at 5 yrs	82% free from LRR at 5 yrs (68% to 90%)	HR 0.35 (0.19 to 0.68)	408 (3 studies)	Very low[1,2,4]
Locoregional recurrence - T stage subgroups - pT0/Tis (7.7 to 10 year follow-up)	71% free from LRR at 7.7 yrs	87% free from LRR at 7.7 yrs (59% to 96%)	HR 0.42 (0.12 to 1.55)	120 (2 studies)	Very low[2]
Locoregional recurrence - T stage subgroups - pT2 (7.7 year follow-up)	85% free from LRR at 7.7yrs	95% free from LRR at 7.7yrs (82% to 99%)	HR 0.33 (0.09 to 1.23)	75 (1 study)	Very low[1,2,5]
Locoregional recurrence - T stage subgroups - pT3 (7.7 year follow-up)	57% free from LRR at 7.7yrs	83% free from LRR at 7.7 yrs (50% to 95%)	HR 0.29 (0.05 to 1.77)	18 (1 study)	Very low[1,2,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: RT-	Corresponding risk: RT+			
Locoregional recurrence - T stage subgroups - pT4 (7.7 year follow-up)	83% free from LRR at 7.7 yrs	72% free from LRR at 7.7 yrs (17% to 94%)	HR 1.8 (0.34 to 9.67)	37 (1 study)	Very low[1,2,5]
Locoregional recurrence - N stage subgroups - cN0 (5 to 10 year follow-up)	60% free from LRR at 5 yrs	85% free from LRR at 5 yrs (70% to 93%)	HR 0.31 (0.14 to 0.69)	196 (3 studies)	Very low[1,2]
Locoregional recurrence - N stage subgroups - cN1 (5 to 10 year follow-up)	71% free from LRR at 5 yrs	87% free from LRR at 5 yrs (77% to 93%)	HR 0.41 (0.22 to 0.78)	467 (3 studies)	Very low[1,2]
Locoregional recurrence - N stage subgroups - cN2 (5 to 7.7 year follow-up)	50% free from LRR at 5 yrs	74% free from LRR at 5 yrs (34% to 92%)	HR 0.43 (0.12 to 1.57)	65 (2 studies)	Very low[1,2,6]
Locoregional recurrence - N stage subgroups - cN2/3 (10 year follow-up)	59% free from LRR at 10 yrs	93% free from LRR at 10 yrs (83% to 97%)	HR 0.13 (0.05 to 0.36)	259 (1 study)	Very low[1,2]
Locoregional recurrence - N stage subgroups - cN3 (5 year follow-up)	0% free from LRR at 5 yrs	Cannot be calculated	HR 0.12 (0 to 5.81)	7 (1 study)	Very low[1,2]
Locoregional recurrence - N stage subgroups - pN0 (4.75 to 10 year follow-up)	91% free from LRR at 4.75 yrs	97% free from LRR at 4.75 yrs (94% to 99%)	HR 0.28 (0.12 to 0.69)	394 (4 studies)	Very low[1,2]
Locoregional recurrence - N stage subgroups - pN1 (7.7 year follow-up)	90% free from LRR at 7.7 yrs	86% free from LRR at 7.7 yrs (58% to 96%)	HR 1.39 (0.38 to 5.15)	63 (1 study)	Very low[1,2,5]
Locoregional recurrence - N stage subgroups - pN2 (7.7 year follow-up)	69% free from LRR at 7.7 yrs	86% free from LRR at 7.7 yrs	HR 0.42 (0.12 to 1.41)	52 (1 study)	Very low[1,2,5]
Locoregional recurrence - N stage subgroups - pN3 (7.7 year follow-up)	85% free from LRR at 7.7 yrs	93% free from LRR at 7.7 yrs (44% to 99%)	HR 0.48 (0.05 to 5.02)	35 (1 study)	Very low[1,2,5]
Locoregional recurrence - T & N stage subgroups - cT3N0 (5 year follow-up)	77% free from LRR at 5 yrs	96% free from LRR at 5 yrs (89% to 99%)	HR 0.15 (0.05 to 0.46)	162 (1 study)	Very low[1,2]
DFS - Whole sample (5 year follow-up)	5 yr DFS 65%	5 yr DFS 81% (59% to 91%)	HR 0.5 (0.21 to 1.21)	161 (1 study)	Very low[1,2]
DFS - pN0 (4.75 to 10 year follow-up)	4.75 yr DFS 83%	4.75 yr DFS 81% (67% to 89%)	HR 1.15 (0.62 to 2.13)	285 (2 studies)	Very low[1,2]
OS - mixed populations (4 to 10 year follow-up)	4 yr OS 54%	4 yr OS 44% (36% to 51%)	HR 1.35 (1.1 to 1.66)	1008 (4 studies)	Very low[1,7]
OS - T stage subgroups - cT1/2 (3.25 year follow-up)	3.25 yr OS 81%	3.25 yr OS 84% (81% to 86%)	HR 0.84 (0.72 to 0.98)	4323 (1 study)	Very low[1,8]
OS - T stage subgroups - cT2 (5 year follow-up)	5 yr OS 73%	5 yr OS 88% (40% to 98%)	HR 0.4 (0.05 to 2.93)	22 (1 study)	Low[-2]
OS - T stage subgroups - cT3 (3.25 to 5 year follow-up)	3.25 yr OS 65%	3.25 yr OS 75% (71% to 78%)	HR 0.68 (0.57 to 0.8)	2956 (2 studies)	Very low[1,8,9]
OS - T stage subgroups - cT4 (5 year follow-up)	5 yr OS 14%	5 yr OS 54% (15% to 82%)	HR 0.31 (0.1 to 0.97)	47 (1 study)	Very low[1,2]
OS - T stage subgroups - pT0/Tis (10 year follow-up)	10 yr OS 25%	10 yr OS 80% (50% to 93%)	HR 0.16 (0.05 to 0.5)	74 (1 study)	Low[-3]
OS - N stage subgroups - cN0 (5 year follow-up)	5 yr OS 0%	Cannot calculate	HR 0.12 (0.02 to 0.63)	14 (1 study)	Very low[1,2]
OS - N stage subgroups - cN1 (5 year follow-up)	5 yr OS 71%	5 yr OS 66% (35% to 85%)	HR 1.21 (0.47 to 3.1)	54 (1 study)	Very low[1,2]
OS - N stage subgroups - cN2 (5 year follow-up)	5 yr OS 25%	5 yr OS 78% (12% to 97%)	HR 0.18 (0.02 to 1.52)	32 (1 study)	Very low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: RT-	Corresponding risk: RT+			
OS - N stage subgroups - cN3 (5 year follow-up)	5 yr OS 0%	Cannot calculate	HR 0.47 (0.04 to 5.79)	7 (1 study)	Very low[1,2]
OS - N stage subgroups - pN0 (4.75 to 10 year follow-up)	4.75 yr OS 89%	4.75 yr OS 87% (83% to 89%)	HR 1.24 (0.97 to 1.6)	285 (3 studies)	Very low[1,2]
OS - N stage subgroups - pN1 (3.25 year follow-up)	3.25 yr OS 82%	3.25 yr OS 85% (82% to 87%)	HR 0.84 (0.71 to 0.98)	4504 (1 study)	Very low[1,8]
OS - N stage subgroups - pN2/3 (3.25 year follow-up)	3.25 yr OS 61%	3.25 yr OS 72% (67% to 75%)	HR 0.68 (0.57 to 0.8)	2739 (1 study)	Very low[1,8]
OS - N stage subgroups - cN1pN0 (5 year follow-up)	5 yr OS 82%	5 yr OS 85% (80% to 88%)	HR 0.83 (0.63 to 1.1)	1181 (1 study)	Very low[1,2]
OS - N stage subgroups - cN2/3pN0 (5 year follow-up)	5 yr OS 82%	5 yr OS 86% (77% to 91%)	HR 0.78 (0.47 to 1.32)	379 (1 study)	Very low[1,2]
OS - T & N stage subgroups - cT1/2pN0 (3.25 to 5 year follow-up)	3.25 yr OS 91%	3.25 yr OS 94% (92% to 95%)	HR 0.69 (0.53 to 0.91)	2498 (2 studies)	Very low[1,2]
OS - T & N stage subgroups - cT3/4pN0 (3.25 to 5 year follow-up)	3.25 yr OS 87%	3.25 yr OS 90% (88% to 92%)	HR 0.73 (0.58 to 0.93)	2102 (2 studies)	Very low[1]
OS - T & N stage subgroups - pT0/TisN0 (5 year follow-up)	5 yr OS 87%	5 yr OS 87% (81% to 91%)	HR 1.03 (0.68 to 1.56)	676 (1 study)	Very low[1,2]
OS - T & N stage subgroups - pT1/2N0 (5 year follow-up)	5 yr OS 78%	5 yr OS 83% (78% to 87%)	HR 0.73 (0.53 to 0.99)	884 (1 study)	Very low[1,2]

Rates of disease-free survival and overall survival in the control group correspond to the trial with the shortest follow-up period
CI: Confidence interval; LRR: locoregional recurrence; OS: overall survival; RR: Risk ratio; HR: Hazard ratio
[1] *Significant differences in patient characteristics between arms for all trials*
[2] *<300 events*
[3] *HR and 95% CI<0.5*
[4] *Significant unexplained heterogeneity; I2 85%. Not possible to explore sources of heterogeneity as additional subgroups of interest identified by the committee were not reported*
[5] *Intervention: 84% received radiotherapy to chest wall and regional nodes; remainder just received radiotherapy to chest wall*
[6] *Intervention: 84% received radiotherapy to chest wall and regional nodes in the trial with the largest weight; remainder just received radiotherapy to chest wall*
[7] *Significant heterogeneity; I2 64%. Explored in subsequent subgroup analysis*
[8] *Intervention: unclear what percentage received radiotherapy to the regional nodes*
[9] *Significant unexplained heterogeneity; I2 76%. Not possible to explore sources of heterogeneity as additional subgroups of interest identified by the committee were not reported*

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy versus no radiotherapy

Critical outcomes

Locoregional recurrence

- There is very low quality evidence from 4 retrospective cohort studies (N=1,008) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful reductions in locoregional recurrence at 4 to 10 year follow-up compared with no radiotherapy for mixed populations of adults with invasive breast cancer.
- There is very low quality evidence from 3 retrospective cohort studies (N=199) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful reductions in locoregional recurrence at 5 to 10 year follow-up compared with no radiotherapy for adults with cT2 invasive breast cancer.
- There is low quality evidence from 3 retrospective cohort studies (N=320) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful reductions in locoregional recurrence at 5 to 10 year follow-up compared with no radiotherapy for adults with cT3 invasive breast cancer.
- There is very low quality evidence from 3 retrospective cohort studies (N=408) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful reductions in locoregional recurrence at 5 to 10 year follow-up compared with no radiotherapy for adults with cT4 invasive breast cancer.
- There is low quality evidence from 2 retrospective cohort studies (N=120) that there is no effect of postmastectomy radiotherapy on locoregional recurrence at 7.7 to 10 year follow-up for adults with pT0/Tis invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=75) that there is no effect of postmastectomy radiotherapy on locoregional recurrence at 7.7 year follow-up for adults with pT2 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=18) that there is no effect of postmastectomy radiotherapy on locoregional recurrence at 7.7 year follow-up for adults with pT3 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=37) that there is no effect of postmastectomy radiotherapy on locoregional recurrence at 7.7 year follow-up for adults with pT4 invasive breast cancer.
- There is very low quality evidence from 3 retrospective cohort studies (N=196) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful reductions in locoregional recurrence at 5 to 10 year follow-up compared with no radiotherapy for adults with cN0 invasive breast cancer.
- There is very low quality evidence from 3 retrospective cohort studies (N=467) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful reductions in locoregional recurrence at 5 to 10 year follow-up compared with no radiotherapy for adults with cN1 invasive breast cancer.

- There is very low quality evidence from 2 retrospective cohort studies (N=65) that there is no effect of postmastectomy radiotherapy on locoregional recurrence at 5 to 7.7 year follow-up for adults with cN2 invasive breast cancer.
- There is low quality evidence from 1 retrospective cohort study (N=259) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for adults with cN2/3 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=7) that there is no effect of postmastectomy radiotherapy on locoregional recurrence at 5 year follow-up for adults with cN3 invasive breast cancer.
- There is very low quality evidence from 4 retrospective cohort studies (N=394) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful reductions in locoregional recurrence at 4.75 to 10 year follow-up compared with no radiotherapy for adults with pN0 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=63) that there is no effect of postmastectomy radiotherapy on locoregional recurrence at 7.7 year follow-up for adults with pN1 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=52) that there is no effect of postmastectomy radiotherapy on locoregional recurrence at 7.7 year follow-up for adults with pN2 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=35) that there is no effect of postmastectomy radiotherapy on locoregional recurrence at 7.7 year follow-up for adults with pN3 invasive breast cancer.
- There is low quality evidence from 1 retrospective cohort study (N=162) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful reductions in locoregional recurrence at 5 year follow-up compared with no radiotherapy for adults with cT3N0 invasive breast cancer.

Disease-free survival

- There is very low quality evidence from 1 retrospective cohort study (N=161) that there is no effect of postmastectomy radiotherapy on disease-free survival at 5 year follow-up for mixed populations of adults with invasive breast cancer.
- There is very low quality evidence from 2 retrospective cohort studies (N=285) that there is no effect of postmastectomy radiotherapy on disease-free survival at 4.75 to 10 year follow-up adults with pN0 invasive breast cancer.

Treatment-related morbidity

- No evidence was found for this outcome.

Important outcomes

Overall survival

- There is very low quality evidence from 4 retrospective cohort studies (N=1008) that there is no effect of postmastectomy radiotherapy on overall survival at 4 to 10 year follow-up for mixed populations of adults with invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=4,323) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful increases in overall survival at 3.25 year follow-up compared with no radiotherapy for adults with cT1/2 invasive breast cancer.

- There is moderate quality evidence from 1 retrospective cohort study (N=22) that there is no effect of postmastectomy radiotherapy on overall survival at 5 year follow-up for adults with cT2 invasive breast cancer.
- There is very low quality evidence from 2 retrospective cohort studies (N=2,956) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful increases in overall survival at 3.25 to 5 year follow-up compared with no radiotherapy for adults with cT3 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=47) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful increases in overall survival at 5 year follow-up compared with no radiotherapy for adults with cT4 invasive breast cancer.
- There is moderate quality evidence from 1 retrospective cohort study (N=74) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful increases in overall survival at 10 year follow-up compared with no radiotherapy for adults with pT0/Tis invasive breast cancer.
- There is low quality evidence from 1 retrospective cohort study (N=14) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful increases in overall survival at 5 year follow-up compared with no radiotherapy for adults with cN0 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=54) that there is no effect of postmastectomy radiotherapy on overall survival at 5 year follow-up for adults with cN1 invasive breast cancer.
- There is low quality evidence from 1 retrospective cohort study (N=32) that there is no effect of postmastectomy radiotherapy on overall survival at 5 year follow-up for adults with cN2 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=7) that there is no effect of postmastectomy radiotherapy on overall survival at 5 year follow-up for adults with cN3 invasive breast cancer.
- There is very low quality evidence from 3 retrospective cohort studies (N=285) that there is no effect of postmastectomy radiotherapy on overall survival at 4.75 to 10 year follow-up for adults with pN0 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=4,504) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful increases in overall survival at 3.25 year follow-up compared with no radiotherapy for adults with pN1 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=2,739) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful increases in overall survival at 3.25 year follow-up compared with no radiotherapy for adults with pN2/3 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=1,181) that there is no effect of postmastectomy radiotherapy on overall survival at 5 year follow-up for adults with cN1pN0 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=379) that there is no effect of postmastectomy radiotherapy on overall survival at 5 year follow-up for adults with cN2/3pN0 invasive breast cancer.
- There is very low quality evidence from 2 retrospective cohort studies (N=2,498) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful increases in overall survival at 3.25 to 5 year follow-up compared with no radiotherapy for adults with cT1/2pN0 invasive breast cancer.
- There is very low quality evidence from 2 retrospective cohort studies (N=2,102) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant

chemotherapy produces clinically meaningful increases in overall survival at 3.25 to 5 year follow-up compared with no radiotherapy for adults with cT3/4pN0 invasive breast cancer.

- There is very low quality evidence from 1 retrospective cohort study (N=676) that there is no effect of postmastectomy radiotherapy on overall survival at 5 year follow-up for adults with pT0/TispN0 invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (N=884) that postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy produces clinically meaningful increases in overall survival at 5 year follow-up compared with no radiotherapy for adults with pT1/2pN0 invasive breast cancer.

Health-related quality of life

- No evidence was found for this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As the aim of the intervention in this review was to prevent disease recurrence, the committee identified locoregional recurrence, disease-free survival and treatment-related morbidity as critical outcomes. Treatment-related morbidity was selected ahead of overall survival, which was identified as an important outcome, due to the significant side effects associated with radiotherapy. Health-related quality of life was also selected as an important outcome as this may be affected by treatment-related morbidities and disruption caused by radiotherapy appointments.

No evidence was identified for treatment-related morbidities or health-related quality of life.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE and was found to be of very low to low quality. The quality for different outcomes is summarised below:

- Disease-free survival: all evidence was very low quality as it was derived from retrospective cohort studies, there were very small number of events of interest (<100), and there were significant differences in the baseline characteristics between arms.
- Locoregional recurrence: all evidence was very low quality as it was derived from retrospective cohort studies, there were very small number of events of interest (<100), and there were significant differences in the baseline characteristics between arms. In addition, there was some indirect evidence as not everyone received radiotherapy to the regional nodes (some just received it to chest wall).
- Overall survival: the vast majority of evidence was very low quality, with some low quality evidence as well, due to the fact it was derived from retrospective cohort studies, there were very small number of events of interest (<100), and there were significant differences in the baseline characteristics between arms. In addition, there was some indirect evidence as not everyone received radiotherapy to the regional nodes (some just received it to chest wall)

Benefits and harms

The evidence demonstrated that there were lower rates of locoregional recurrence following postmastectomy radiotherapy for the mixed population and the majority of clinical subgroups examined; however, this was not the case for subgroups based on pathological T and N stages. For overall survival, there was no evidence for an improved outcome in the mixed

population, and the evidence for the clinical and pathological subgroups was varied, with little evidence for improved survival in the nodal subgroups.

The committee agreed that the benefit of recommendations would be appropriate use of postmastectomy radiotherapy (although the majority of centres already offer radiotherapy in accordance with the recommendations), thus leading to reduced locoregional recurrence and improved overall survival.

Although no evidence was found on the adverse effects of radiotherapy, the Committee knew from their clinical experience that the potential harm of the recommendations would include the likely significant side-effects of radiotherapy.

The committee also discussed the possibility of over-treatment as the recommendations would lead to all people with nodal involvement (based on pre-treatment investigations) who had received neoadjuvant chemotherapy receiving radiotherapy. The evidence suggests that individuals who are pT0/Tis/pN0 don't benefit from postmastectomy radiotherapy, and this may be the stage of these people after neoadjuvant chemotherapy and surgery. However, due to the very low quality of the evidence, the committee were not confident that this group could safely be excluded from treatment.

The evidence showed a benefit in terms of locoregional recurrence (LRR) and overall survival (OS) for cT1/2 tumours (additional 3% alive at 3.25 years and 23% free from LRR at 5 years); however, the evidence was very low quality and based on small sample sizes so the committee did not think there was sufficient evidence of benefit to include this subgroup in the recommendations. It is worth noting, however, that it was unclear from the evidence if the cT1/2 tumours were node negative or node positive; the latter group would also be covered by the current recommendations.

The committee balanced the harms and benefits of the recommendations and agreed that people prioritise reduced recurrence and overall survival over the short-term detrimental effects of radiotherapy. In addition, the committee were aware that radiotherapy techniques are improving all the time in the UK, with extensive quality assurance programmes ensuring clinical practices are constantly refined to reduce the number and severity of side-effects.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee discussed the potential costs and savings associated with the recommendations and agreed that there would be no resource implications. In current practice (based on the previous NICE guideline GC80), all people who are high risk for local recurrence (based on pre-treatment investigations) receive post mastectomy radiotherapy. The intention of this review was to ascertain whether a subgroup of people could be identified that will not benefit from post mastectomy radiotherapy (in whom radiotherapy could then be omitted). Since no such subgroup was identified, the committee have maintained that those who receive neoadjuvant chemotherapy should receive radiotherapy in line with those who have not received neoadjuvant chemotherapy. Therefore no changes in costs and savings are anticipated.

Other factors the committee took into account

The committee discussed the fact that the review question was about 'neoadjuvant systemic therapy'. However, all evidence available was for neoadjuvant chemotherapy, and therefore the recommendations could only relate to the use of chemotherapy and could not be generalised to include people who had received neoadjuvant endocrine therapy or monoclonal antibody treatment.

Due to very low quality evidence and the inconsistent results the committee did not think there was sufficient evidence to conclude in which groups of people who received neoadjuvant chemotherapy, postmastectomy radiotherapy could be safely omitted. Therefore, the committee agreed the decision whether or not to offer postmastectomy radiotherapy should be based on the same criteria as for those who have not received neoadjuvant chemotherapy as this evidence base is larger, more established and based on RCTs (see recommendations on postmastectomy radiotherapy in evidence report H); this criteria should be applied to both pre-treatment investigations and post-surgical histology.

Due to the lack of good quality evidence for this review question the committee made a research recommendation for randomised controlled trials examining indications for postmastectomy radiotherapy after neoadjuvant chemotherapy.

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Review question 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

Introduction

Neoadjuvant chemotherapy for triple negative breast cancer and BReast CAncer (BRCA) germ line mutation carriers include anthracycline- and taxane-containing regimens. The addition of platinum salts to these regimens may improve the response to chemotherapy. Better response rates improve successful resection at surgery for locally advanced breast cancer, and for triple negative breast cancer complete pathological response rates (no detectable breast cancer on final standard pathology at surgery, pCR) are associated with reduced risk of breast cancer recurrence, and improved survival. However, the addition of platinum increases the side effects of the regimen.

The aim of this review is to assess the role of addition of platinum agents to anthracycline ± taxane based neoadjuvant chemotherapy in women with triple negative/BRCA germ line mutation.

PICO table

See Table 12 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 12: Summary of the protocol (PICO table)

Population	Adults (18 or over) with triple negative or BRCA germ line mutation with invasive breast cancer receiving primary chemotherapy
Intervention	Platinum containing regimen
Comparison	Non-platinum containing regimen
Outcome	**Critical** • Pathological complete response rate • Overall survival • Disease-free survival **Important** • Overall response rate • Adequate dose intensity • Breast conservation rate • Local recurrence rate • Treatment-related morbidity • Treatment-related mortality • HRQoL

HRQoL: Health related quality of life

For full details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Five randomized controlled trials (n=1007) identified by the literature search were included in the review (Alba 2012; Ando 2014; Sikov 2015; Von Minckwitz 2014; Zhang 2016). All 5 studies reported on pathological complete response rate. One study reported on overall and disease free survival at 5 years. Two studies reported on overall response rate, breast conservation rate and three studies reported on treatment related morbidities. One study reported on treatment related mortality and there was no evidence available for adequate dose intensity, local recurrence rate or health related quality of life.

The clinical studies included in this evidence review are summarised in Table 13 and evidence from these are summarised in the clinical GRADE evidence profile below (Table 3. See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 13: Summary of included studies

Study	Additional inclusion/exclusion criteria	Interventions/comparison
Alba 2012	• Age <75 years • Basal like carcinoma	• Intervention arm: Epirubicin 90mg/m^2 + cyclophosphamide 600mg/m^2 (q 21 days x 4 courses) followed by docetaxel 75mg/m^2 + carboplatin AUC 6 mg/ml/min (q 21 days x 4 courses) • Control arm: Epirubicin 90mg/m^2 + cyclophosphamide 600mg/m^2 (q 21 days x 4 courses) followed by Docetaxel 100mg/m^2 (q 21 days x 4 courses)
Ando 2014	• No additional criteria	• Intervention group: Four 3-week cycles of carboplatin [area under the curve 5 mg/mL/min, day 1] and weekly paclitaxel [80 mg/m^2, day 1, 8, 15] followed by four 3-week cycles of cyclophosphamide, epirubicin and 5-flourouracil [500/100/500 mg/m^2] • Control group: Four cycles of weekly paclitaxel followed by four cycles of cyclophosphamide, epirubicin and 5-flourouracil [500/100/500 mg/m^2].
Sikov 2015	• No additional criteria	• Control arm: paclitaxel 80mg/m^2 once per week (wP) for 12 weeks followed by doxorubicin 60mg/m^2 • and cyclophosphamide 600 mg/m^2 once every 2 weeks with myeloid growth factor support (ddAC) for four cycles. • Intervention arm: carboplatin at an area-under-the curve (AUC) dose of 6 once every 3 weeks for four cycles in

Study	Additional inclusion/exclusion criteria	Interventions/comparison
		addition to paclitaxel 80 mg/m² once per week (wP) for 12 weeks followed by doxorubicin 60mg/m² and cyclophosphamide 600 mg/m² once every 2 weeks with myeloid growth factor support (ddAC) for four cycles
Von Minckwitz 2014	• No additional criteria	• Intervention: Paclitaxel 80 mg/m² plus non-pegylated liposomal doxorubicin 20 mg/m², both given once a week for 18 weeks. Bevacizumab 15 mg/kg intravenously every 3 weeks simultaneously with all cycles. • Carboplatin at a dose of 2.0 area under curve (AUC), once every week for 18 weeks. Dose reduced to AUC 1.5 after an interim safety analysis. The dose of carboplatin could be reduced to AUC 1.1 in case of intolerable toxic effects. • Control: Paclitaxel 80 mg/m² plus non-pegylated liposomal doxorubicin 20 mg/m², both given once a week for 18 weeks. Bevacizumab 15 mg/kg intravenously every 3 weeks simultaneously with all cycles
Zhang 2016	• No additional criteria	• Intervention arm: Paclitaxel 175 mg/m² on day 1 plus carboplatin Area Under the Curve (AUC) = 5 on day 2, both administered via intravenous infusion (IV),every 3 weeks for 4-6 cycles. • Control arm: Epirubicin 75 mg/m² on day 1 and paclitaxel 175 mg/m² on day 2, both IV, every 3 weeks for 4-6 cycles.

AUC,Area under curve; ddAC, Dose dense doxorubicin & cyclophosphamide; wP, weekly paclitaxel; IV, intravenous

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (platinum vs non-platinum regimens with anthracyclines ± taxane based neoadjuvant therapy for triple negative/BRCA germ line mutation) is presented in Table 3. The included evidence was of low to very low quality. Main reasons for downgrading evidence was imprecision around the estimates due to a small number of events of interest and wide confidence intervals, indirectness and risk of bias due to unavailability of data regarding comparability between groups at baseline.

Table 14: Summary clinical evidence profile: Comparison 1. Platinum containing regimen vs non-platinum containing regimen in adults with triple negative invasive breast cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Non platinum NAC	Platinum NAC			
Pathological complete response rate PCR at surgery	378 per 1000	533 per 1000 (465 to 613)	RR 1.41 (1.23 to 1.62)	1007 (5 studies[1,2,3,4,5])	Low[6,7,8]
Overall Survival - 5 year overall survival Follow-up: median 55 months	705 per 1000	831 per 1000 (655 to 1000)	RR 1.18 (0.93 to 1.48)	91 (1 study[1])	Low[9]
Disease-free survival 5 year relapse free survival Follow-up: median 55 months	568 per 1000	767 per 1000 (568 to 1000)	RR 1.35 (1 to 1.82)	91 (1 study[1])	Low[9]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Non platinum NAC	Platinum NAC			
Overall response rate ORR after treatment	744 per 1000	826 per 1000 (715 to 960)	RR 1.11 (0.96 to 1.29)	184 (2 studies[1,4])	Very low[8,9]
Breast conservation rate	481 per 1000	596 per 1000 (509 to 702)	RR 1.24 (1.06 to 1.46)	526 (2 studies[4,5])	Low[8,10]
Treatment related morbidity - Grade 3/4 Adverse events	306 per 1000	377 per 1000 (300 to 478)	RR 1.23 (0.98 to 1.56)	526 (2 studies[4,5])	Very low[9,11]
Treatment related morbidity - Anaemia	8 per 1000	43 per 1000 (11 to 164)	RR 5.6 (1.48 to 21.16)	526 (2 studies[4,5])	Very low[9,11]
Treatment related morbidity - Leucopenia	112 per 1000	164 per 1000 (106 to 254)	RR 1.46 (0.94 to 2.26)	526 (2 studies[4,5])	Very low[9,11]
Treatment related morbidity - Neutropenia	318 per 1000	550 per 1000 (458 to 658)	RR 1.73 (1.44 to 2.07)	617 (3 studies[1,4,5])	Very low[11,12]
Treatment related morbidity - Thrombocytopenia	30 per 1000	199 per 1000 (103 to 385)	RR 6.68 (3.46 to 12.92)	617 (3 studies[1,4,5])	Very low[11,12]
Treatment related morbidity - Febrile neutropenia	89 per 1000	153 per 1000 (94 to 248)	RR 1.72 (1.06 to 2.78)	526 (2 studies[4,5])	Very low[8,11,12]
Treatment related morbidity - Hypersensitivity	43 per 1000	21 per 1000 (2 to 227)	RR 0.49 (0.05 to 5.21)	93 (1 study[4])	Very low[8,9]
Treatment related morbidity - Fatigue	112 per 1000	130 per 1000 (82 to 208)	RR 1.16 (0.73 to 1.85)	526 (2 studies[4,5])	Very low[9,11]
Treatment related morbidity - Infection	87 per 1000	85 per 1000 (23 to 320)	RR 0.98 (0.26 to 3.68)	93 (1 study[4])	Very low[9,10]
Treatment related morbidity - Diarrheoa	14 per 1000	23 per 1000 (6 to 94)	RR 1.6 (0.39 to 6.61)	433 (1 study[5])	Very low[9,11]
Treatment related morbidity - Hypertension	66 per 1000	46 per 1000 (20 to 100)	RR 0.69 (0.31 to 1.51)	433 (1 study[5])	Very low[9,11]
Treatment related morbidity - ALT/AST elevation	66 per 1000	66 per 1000 (37 to 117)	RR 1 (0.56 to 1.76)	524 (2 studies[1,5])	Very low[9,11]
Treatment related morbidity - Peripheral neuropathy	98 per 1000	110 per 1000 (70 to 174)	RR 1.13 (0.72 to 1.78)	524 (2 studies[1,5])	Very low[9,11]
Treatment related morbidity - ST-T changes	250 per 1000	192 per 1000 (87 to 417)	RR 0.77 (0.35 to 1.67)	91 (1 study[1])	Very low[8,10]
Treatment related mortality	0 per 1000	0 per 1000 (0 to 0)	RR 2.88 (0.12 to 70.27)	433 (1 study[5])	Very low[9,11]

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CI: confidence interval; NAC: Neoadjuvant chemotherapy; ORR: Overall response rate; pCR: Pathological complete response; RR: risk ratio; TNBC: Triple Negative Breast Cancer

[1] Zhang 2016

[2] Ando 2014

[3] Von Minckwitz 2014

[4] Alba 2012

[5] Sikov 2014

[6] downgraded by 1 level for serious risk of bias. TNBC is a subgroup in Ando 2014 and Von Minckwitz 2014 .segregated information is not available regarding comparability of intervention and control groups at baseline

[7] *serious inconsistency. I square =56%.*
[8] *downgraded by 1 level for serious indirectness. Alba 2012 is restricted to patients with basal like breast cancer*
[9] *downgraded by 2 levels for very serious imprecision ;<300 events;95% ci crosses limits for no effect.*
[10] *downgraded by 1 level for serious imprecision; 95% ci crosses limits for no effect*
[11] *downgraded by 1 level for serious indirectness due to simultaneous treatment with bevacizumab*
[12] *downgraded by 1 level for serious imprecision; < 300 events*

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Platinum containing regimen vs non-platinum containing regimen in people with triple negative invasive breast cancer

Critical outcomes

Pathological complete response

- There is low quality evidence from 5 RCTs (N=1007) that addition of platinum to anthracyclines ± taxane based neoadjuvant chemotherapy produces clinically meaningful increases in pathological complete response rate at surgery for people with triple negative invasive breast cancer.

Overall survival

- There is low quality evidence from 1 RCT *(*N=91) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on overall survival at 5 years for people with triple negative invasive breast cancer.

Disease-free survival

- There is low quality evidence from 1 RCT (N=91) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on relapse-free survival at 5 years for people with triple negative invasive breast cancer.

Important outcomes

Overall response rate

- There is very low quality evidence from 2 RCTs (N=184) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on overall response rate for people with triple negative invasive breast cancer.

Adequate dose intensity

- No evidence was found for this outcome.

Breast conservation rate

- There is low quality evidence from 2 RCTs (N=526) that there is no clinically important effect of addition of platinum to anthracyclines ± taxane based neoadjuvant chemotherapy

on breast conservation rate at surgery for people with triple negative invasive breast cancer.

Local recurrence rate

- No evidence was found for this outcome.

Treatment-related morbidity

- There is very low quality evidence from 2 RCTs (N=526) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on Grade 3/4 adverse events for people with triple negative invasive breast cancer.
- There is very low quality evidence from 2 RCTs (N=526) there is clinically significant increase in anaemia on addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy for people with triple negative invasive breast cancer.
- There is very low quality evidence from 2 RCTs (N=526) there is clinically significant increase in febrile neutropenia on addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy for people with triple negative invasive breast cancer.
- There is very low quality evidence from 3 RCTs (N=617) there is clinically significant increase in neutropenia on addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy for people with triple negative invasive breast cancer.
- There is very low quality evidence from 3 RCTs (N=617) there is clinically significant increase in thrombocytopenia on addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy for people with triple negative invasive breast cancer.
- There is very low quality evidence from 2 RCTs (N=526) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on leucopenia for people with triple negative invasive breast cancer.
- There is very low quality evidence from (1 RCT, N=93) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on hypersensitivity for people with triple negative invasive breast cancer.
- There is very low quality evidence from 2 RCTs (N=526) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on fatigue for people with triple negative invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=93) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on infection for people with triple negative invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=433) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on hypertension for people with triple negative invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=433) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on diarrhoea for people with triple negative invasive breast cancer.
- There is very low quality evidence from 2 RCTs (N= 524) that there is no clinically important effect of addition of platinum to anthracycline ±taxane based neoadjuvant chemotherapy on ALT/AST elevation for people with triple negative invasive breast cancer.
- There is very low quality evidence from (1 RCT, N=433) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on diarrhoea for people with triple negative invasive breast cancer.
- There is very low quality evidence from 2 RCTs (N= 524) that there is no clinically important effect of addition of platinum to anthracycline ±taxane based neoadjuvant

chemotherapy on peripheral neuropathy for people with triple invasive negative breast cancer.

Treatment-related mortality

- There is very low quality evidence from 1 RCTs (N=433) that there is no clinically important effect of addition of platinum to anthracycline ± taxane based neoadjuvant chemotherapy on treatment related mortality for people with triple negative invasive breast cancer.

Health-related quality of life

- No evidence was found for this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As this review question is considering a treatment used before surgery to shrink a tumour, pathological complete response rate, overall survival and disease-free survival were selected as critical outcomes by the committee. The inclusion of treatment-related morbidities and treatment-related mortality as important outcomes was to allow a balance of the benefits and harms of treatments to be made. Overall response rate, adequate dose intensity, breast conservation rate, local recurrence rate and health related quality of life were identified as other important outcomes.

Survival outcomes are prioritised by patients; however, treatment-related morbidities are also important to patients as they affect patients' acceptance of, and adherence to, treatment.

No evidence was available for adequate dose intensity, health-related quality of life and local recurrence rate. Additionally, there was no evidence regarding the BRCA germ line mutation subgroup.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. For pCR the evidence was of low quality, and was downgraded due risk of bias (due to a lack of information for the triple negative subgroup at baseline in two studies) and due to indirectness (due to inclusion of basal-like tumours in another study). For overall survival with platinum-based neoadjuvant chemotherapy compared to anthracycline-based neoadjuvant chemotherapy, the evidence was of low quality due to due to small number of events of interest and wide confidence intervals

For disease free survival the evidence was of low quality. There was very serious imprecision and only a small number of events of interest were reported for the study population.

The quality of evidence for overall response rate was very low quality. The evidence quality was downgraded mainly due to uncertainty around the estimate due to small number of events of interest, wide confidence intervals and indirectness due to the inclusion of basal-like tumours.

Breast conservation rate evidence was low quality due to indirectness and imprecision due to small number of events of interest. Treatment-related morbidities evidence was very low quality, mainly due to indirectness and imprecision around outcome. Treatment-related mortality evidence was very low quality due to small number of events, indirectness and imprecision.

There was evidence that platinum based neoadjuvant regimens can lead to a statistically significant increase in breast conservation rates in people with triple negative invasive breast cancer, although this increase did not meet the pre-specified GRADE minimally important difference (MID) default values of clinical significance. However, the committee considered this increase was important to consider when making their recommendations, as it was associated with a number needed to treat (NNT) of 8, meaning for every eight people receiving a platinum based neoadjuvant regimen, one additional breast will be conserved.

Benefits and harms

The addition of platinum agents to anthracycline ± taxane based neoadjuvant chemotherapy leads to improved pCR rate in people with triple negative early and locally advanced breast cancer. Specifically, an additional 15% of people would achieve pCR at surgery compared to non-platinum neoadjuvant chemotherapy. Improved pCR rate can be a surrogate marker of improved long-term outcomes in triple negative breast cancer Also, for every 8 people with triple negative early and locally advanced breast cancer treated with platinum based neoadjuvant chemotherapy, one additional breast can be conserved at surgery.

By treating people with platinum based neoadjuvant chemotherapy, however, there is a risk of people suffering adverse effects. There is an increased incidence of anaemia, thrombocytopenia, neutropenia and febrile neutropenia. The committee noted that elderly patients who already have impaired bone marrow and renal function, those with multiple comorbidities or who are frail may be particularly at increased risk of such adverse effects and hence patients should be carefully selected.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee discussed that there may be additional costs as a result of these recommendations, due to the additional cost of the drug and the costs associated with managing toxicity. Additional costs for delivering the drug would not be anticipated however because platinum chemotherapy would be scheduled at the same time as other chemotherapy and so would not require additional hospital appointments. Therefore the overall increase in costs when adding platinum chemotherapy would not be substantial as the additional drug costs are relatively small. Furthermore, the additional upfront cost of chemotherapy should be offset, at least partially, by potential savings downstream through the avoidance of recurrence. Therefore, it is likely that the addition of platinum based chemotherapy would be cost-effective in cost per QALY terms.

When considering the overall the resource impact for the NHS, the committee agreed that, while the recommendation may require an increase in resources, the increase is unlikely to be significant. This is based on the relatively small increase in treatment costs when adding platinum chemotherapy as well as the fact that some centres are already offering this treatment.

Other factors the committee took into account

The committee noted that there was no prospective randomised evidence for women with BRCA germ line mutation, and so were unable to make a specific recommendation for this group. The committee was aware of the data for platinum therapy in people with metastatic disease, but could not extrapolate for people with early disease. The committee considered making a research recommendation, but agreed that the population of people with BRCA germ line mutation is very small and that it was unlikely a study would ever recruit enough patients to produce a meaningful result.

There was evidence that platinum based neoadjuvant regimens can bring statistically significant increase in breast conservation rates in people with triple negative invasive breast cancer. Although this increase did not meet GRADE MID default values of clinical significance, this change was considered important, given the number needed to treat (NNT) of 8, which means for every eight people receiving platinum based neoadjuvant regimen, one additional breast will be conserved.

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Appendices

Appendix A – Review protocols

Review protocol for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

Field (based on PRISMA-P)	Content
Review question	What is the effectiveness of neoadjuvant chemotherapy?
Type of review question	Intervention review
Objective of the review	The objective of this review is to determine if neoadjuvant chemotherapy (± biological therapy) is clinically and cost effective. Recommendations will aim to cover which subgroups should be offered this treatment.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive breast cancer (M0) who are planned to have surgery
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Anthracycline containing neoadjuvant chemotherapy regimens ± biological therapy
Eligibility criteria – comparator(s)/control or reference (gold) standard	No neoadjuvant chemotherapy ± biological therapy
Outcomes and prioritisation	• Critical (up to 3 outcomes) • Local recurrence (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference) • Important but not critical • Pathological complete response (MID: GRADE default values) • Breast-conservation rate (MID: GRADE default values) • Overall survival (MID: any statistically significant difference) • Response rates (MID: GRADE default values) • The longest follow-up periods will be prioritised for survival and recurrence outcomes if multiple time points are reported.
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs

Field (based on PRISMA-P)	Content
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups (for critical outcomes only): • Surgery vs no surgery (actual rather than treatment intent) • Grade (1/2/3) • ER status (+/-) • HER2 status (+/-) • Triple negative (yes/no) • Histological subtype
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this question as it is a straightforward intervention review limited to RCTs.
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. Due to substantial changes in the focus of the question, searches will be undertaken from 1998 onwards, when NSABP B18 first reported, rather than from 2008. A general exclusions filter and methodological filters (RCT and systematic review) will be used as it is an intervention question.
Identify if an update	Previous question: What is the role of primary systemic treatment in patients with early, invasive breast cancer? Date of search: 28/02/2008 Relevant recommendation(s) from previous guideline: 1) Treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic

Field (based on PRISMA-P)	Content
	therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery. 2) Preoperative systemic therapy can be offered to patients with early invasive breast cancer who are considering breast conserving surgery that is not advisable at presentation. However, the increased risk of local recurrence with breast conserving surgery and radiotherapy rather than mastectomy after systemic therapy should be discussed with the patient.
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables) of the guideline.
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter of the guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P)	Content
	Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; ER, oestrogen receptor; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HER2, human epidermal growth factor receptor 2; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; RT, radiotherapy

Review protocol for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

Field (based on PRISMA-P)	Content
Review question	Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?
Type of review question	Intervention review
Objective of the review	This review aims to confirm whether neo-adjuvant endocrine therapy is safe and effective at increasing breast conservation rates. Recommendations will cover whether neoadjuvant endocrine therapy should be offered, if so to which groups and for what duration.
Eligibility criteria – population/disease/condition/issue/domain	People (18 or over) with ER+ / HER 2 unknown or HER2- invasive breast cancer (M0) who have not yet undergone surgery
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Neoadjuvant endocrine therapy
Eligibility criteria – comparator(s)/control or reference (gold) standard	• No neoadjuvant endocrine therapy • Neoadjuvant chemotherapy
Outcomes and prioritisation	• Critical (up to 3 outcomes) • Disease-free survival (MID: any statistically significant difference) • Breast conservation rates (MID: GRADE default values) • Changes in tumour size (MID: GRADE default values) • Important but not critical • Overall survival (MID: any statistically significant difference) • Local recurrence following surgery (MID: any statistically significant difference) • HRQoL (MID: values from the literature where available, otherwise GRADE default values) • Data from the time point of surgery will be prioritised for breast conservation rates and changes in tumour size. 5 year follow-up periods will be prioritised for the remaining outcomes. • HRQoL MID values from the literature: • FACT-G total: 3-7 points

Field (based on PRISMA-P)	Content
	• 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
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs • Controlled, non-randomised studies (only if RCTs unavailable or insufficient data to inform decision making; treatment duration minimum of 3 months)
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/sub-group analysis, or meta-regression	• Subgroups (for critical outcomes only): • Grade • Menopausal status (pre/post)
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this question as it is a straightforward intervention review.
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate.
Identify if an update	N/A
Author contacts	For authors please see the guideline in development page.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables)..
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual
Criteria for quantitative synthesis	The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

Field (based on PRISMA-P)	Content
Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

ANC, axillary node clearance; BCS, breast cancer subscale; ER, oestrogen receptor; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HER2, human epidermal growth factor recetor 2; HRQoL, health-related quality of life; M0, no distant metastases; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; RT, radiotherapy; SLNB, sentinel lymph node biopsy; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Review protocol for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

Field (based on PRISMA-P)	Content
Review question	What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?
Type of review question	Intervention review
Objective of the review	The objective of this review is to define indications for post mastectomy radiotherapy following primary medical treatment. Recommendations will aim to cover which groups should be offered such treatment.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive breast cancer (M0) who have undergone neoadjuvant systemic therapy and mastectomy
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Radiotherapy to the chest wall • Radiotherapy to the chest wall and regional nodes
Eligibility criteria – comparator(s)/control or reference (gold) standard	No radiotherapy
Outcomes and prioritisation	• Critical (up to 3 outcomes) • Locoregional recurrence rate (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference) • Treatment-related morbidity (MID: GRADE default values) • Important but not critical • Overall survival (MID: any statistically significant difference) • HRQoL (MID: values from the literature where available, otherwise GRADE default values) • The longest follow-up period will be prioritised if multiple time points are reported. • HRQoL MID values from the literature: • 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

Field (based on PRISMA-P)	Content
	• WHOQOL-100: 1 point
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs • Controlled, non-randomised studies (only if RCTs unavailable or insufficient data to inform decision making) • Case series (study population >100)
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/sub-group analysis, or meta-regression	• Subgroups (for critical outcomes only, excluding treatment-related morbidity): • Clinical node stage (pre-chemo) • Clinical T stage (pre-chemo) • Pathological node stage (post-chemo) • Pathological T stage (post-chemo) • Margin status (positive for invasive disease, positive for DCIS, negative)
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this question as it is a straightforward intervention review.
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. Searches will be undertaken from 1990 when the first neoadjuvant studies were reported.
Identify if an update	N/A

Field (based on PRISMA-P)	Content
Author contacts	For authors please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and

Field (based on PRISMA-P)	Content
	drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; chemo, chemotherapy; DCIS, ductal carcinoma in situ; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; M0, no distant metastases; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; RT, radiotherapy; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Review protocol for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

Field (based on PRISMA-P)	Content
Review question	Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neo-adjuvant chemotherapy?
Type of review question	Intervention review
Objective of the review	The objective of this review is to determine whether the addition of platinum chemotherapy to standard neo-adjuvant chemotherapy is clinically and cost-effective. Recommendations will cover if, and to which groups, such treatment should be offered.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with triple negative or BRCA germ line mutation with invasive breast cancer receiving primary chemotherapy
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Platinum containing regimen
Eligibility criteria – comparator(s)/control or reference (gold) standard	Non-platinum containing regimen
Outcomes and prioritisation	Critical (up to 3 outcomes) • Pathological complete response rate (MID: GRADE default values) • Overall survival (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference) Important but not critical • Overall response rate (MID: GRADE default values) • Adequate dose intensity (MID: GRADE default values) • Breast conservation rate (MID: GRADE default values) • Local recurrence rate (MID: any statistically significant difference) • Treatment-related morbidity (MID: GRADE default values) • Treatment-related mortality (MID: any statistically significant difference) • HRQoL (MID: values from the literature where available; GRADE default value for FACT-B endocrine scale) • Longest follow-up periods will be prioritised if multiple time points are reported.

Field (based on PRISMA-P)	Content
	MID values from the literature: • HRQoL: • 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
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/sub-group analysis, or meta-regression	• Subgroups (for critical outcomes only): • Triple negative status • BRCA mutation
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this review question as it is a straightforward intervention review.
Data management (software)	Study sifting will be performed using EndNote. Data extraction will be undertaken in Microsoft Excel. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. Searches will be undertaken from 1995 when the first studies including platinum agents in neoadjuvant chemotherapy for breast cancer were published. A general exclusions filter and methodological filters (RCT and systematic review) will also be used as it is an intervention question.
Identify if an update	N/A

Field (based on PRISMA-P)	Content
Author contacts	For authors please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; M0, no distant metastases; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Appendix B – Literature search strategies

Literature search strategies for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 September 27**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 28 September 2017

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz

#	Searches
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	Neoadjuvant Therapy/ use prmz
34	neoadjuvant therapy/ use oemezd
35	neoadjuvant$.mp.
36	(primary adj3 (chemotherap$ or therap$ or treatment$)).mp.
37	(induct$ adj3 (chemotherap$ or therap$ or treatment$)).mp.
38	((perioperat$ or peri-operat$ or peri operat$ or perisurg$ or peri-surg$ or peri surg$ or preoperat$ or pre-operat$ or presurg$ or pre-surg$) adj3 (chemotherap$ or therap$ or treatment$)).mp.
39	(initial adj3 (therap$ or treatment$)).mp.
40	(primary adj3 surg$).mp.
41	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42	32 and 41
43	exp Anthracyclines/ use prmz
44	exp anthracycline/ use oemezd
45	doxorubicin/ use oemezd
46	epirubicin/ use oemezd
47	idarubicin/ use oemezd
48	daunorubicin/ use oemezd
49	Mitoxantrone/ use prmz
50	mitoxantrone/ use oemezd
51	anthracyclin$.mp.
52	(doxorubicin$ or adriamycin$ or doxil or caelyx or myocet or rubex or epirubicin$ or ellence or idarubicin$ or Zavedos or daunorubicin$ or daunomycin$ or cerubidin$ or mitoxantron$ or novantrone).mp.
53	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54	42 and 53
55	(anthracyclin$ or doxorubicin$ or adriamycin$ or doxil or caelyx or myocet or rubex or epirubicin$ or ellence or idarubicin$ or Zavedos or daunorubicin$ or daunomycin$ or cerubidin$ or mitoxantron$ or novantrone).m_titl.
56	(mastectom$ or mammectom$ or surg$).m_titl.
57	32 and 55 and 56
58	54 or 57
59	limit 58 to yr="1997 -Current"
60	remove duplicates from 59
61	Limit 60 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

Date of last search: 28 September 2017

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Neoadjuvant Therapy] explode all trees
#23	neoadjuvant*:ti,ab,kw (Word variations have been searched)
#24	((perioperat* or peri-operat* or peri operat* or perisurg* or peri-surg* or peri surg* or preoperat* or pre-operat* or presurg* or pre-surg* or primary or induct*) near/3 (chemotherap* or therap* or treatment*)):ti,ab,kw (Word variations have been searched)
#25	((primary or induct*) near/3 (chemotherap* or therap* or treatment*)):ti,ab,kw (Word variations have been searched)
#26	(initial near/3 (therap* or treatment*)):ti,ab,kw (Word variations have been searched)
#27	(primary near/3 surg*):ti,ab,kw (Word variations have been searched)
#28	#22 or #23 or #24 or #25 or #26 or #27
#29	MeSH descriptor: [Anthracyclines] explode all trees
#30	MeSH descriptor: [Mitoxantrone] explode all trees
#31	(anthracycline* or doxorubicin* or adriamycin* or doxil or caelyx or myocet or rubex or epirubicin* or ellence or idarubicin* or Zavedos or daunorubicin* or daunomycin* or cerubidin* or mitoxantron* or novantrone):ti,ab,kw (Word variations have been searched)
#32	#29 or #30 or #31
#33	#21 and #28 and #32

#	Searches
#34	(anthracycline* or doxorubicin* or adriamycin* or doxil or caelyx or myocet or rubex or epirubicin* or ellence or idarubicin* or Zavedos or daunorubicin* or daunomycin* or cerubidin* or mitoxantron* or novantrone):ti (Word variations have been searched)
#35	(mastectom* or mammectom* or surg*):ti,ab,kw (Word variations have been searched)
#36	#21 and #34 and #35
#37	#33 or #36

Literature search strategies for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 September 28**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 29 September 2017

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz

#	Searches
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	Neoadjuvant Therapy/ use prmz
34	neoadjuvant therapy/ use oemezd
35	neoadjuvant$.tw.
36	(primary adj3 (chemotherap$ or therap$ or treatment$)).tw.
37	(induct$ adj3 (chemotherap$ or therap$ or treatment$)).tw.
38	((perioperat$ or peri-operat$ or peri operat$ or perisurg$ or peri-surg$ or peri surg$ or preoperat$ or pre-operat$ or presurg$ or pre-surg$) adj3 (chemotherap$ or therap$ or treatment$)).tw.
39	33 or 34 or 35 or 36 or 37 or 38
40	32 and 39
41	exp Aromatase Inhibitors/ use prmz
42	exp aromatase inhibitor/ use oemezd
43	aromatase inhibitor$.mp.
44	anastrazole.mp.
45	arimidex.mp.
46	letrozole.mp.
47	femara.mp.
48	exemestane.mp.
49	aromasin.mp.
50	Tamoxifen/ use prmz
51	tamoxifen/ use oemezd
52	(Nolvadex or tamoxifen$).mp.
53	41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54	40 and 53
55	((perioperat$ or peri-operat$ or peri operat$ or perisurg$ or peri-surg$ or peri surg$ or preoperat$ or pre-operat$ or presurg$ or pre-surg$) adj3 (tamoxifen$ or aromatase$ or AI$)).tw.
56	32 and 55
57	54 or 56
58	(initial adj3 (therap$ or treatment$)).tw.
59	(primary adj3 surg$).tw.
60	58 or 59
61	32 and 53 and 60
62	(aromatase inhibitor$ or anastrazole or arimidex or letrozole or femara or exemestane or aromasin or Nolvadex or tamoxifen$).m_titl.
63	(mastectom$ or mammectom$ or surg$).m_titl.
64	32 and 62 and 63
65	57 or 61 or 64
66	limit 65 to yr="1997 -Current" [Then general exclusions filter applied]

Database: Cochrane Library via Wiley Online

Date of last search: 29 September 2017

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Neoadjuvant Therapy] explode all trees
#23	neoadjuvant*:ti,ab,kw (Word variations have been searched)
#24	((perioperat* or peri-operat* or peri operat* or perisurg* or peri-surg* or peri surg* or preoperat* or pre-operat* or presurg* or pre-surg* or primary or induct*) near/3 (chemotherap* or therap* or treatment*)):ti,ab,kw (Word variations have been searched)
#25	((primary or induct*) near/3 (chemotherap* or therap* or treatment*)):ti,ab,kw (Word variations have been searched)
#26	#22 or #23 or #24 or #25
#27	MeSH descriptor: [Aromatase Inhibitors] explode all trees
#28	aromatase inhibitor*:ti,ab,kw (Word variations have been searched)
#29	(anastrazole or arimidex or letrozole or femara or exemestane or aromasin):ti,ab,kw (Word variations have been searched)
#30	MeSH descriptor: [Tamoxifen] this term only
#31	(Nolvadex or tamoxifen*):ti,ab,kw (Word variations have been searched)
#32	#27 or #28 or #29 or #30 or #31
#33	#21 and #26 and #32

#	Searches
#34	((perioperat* or peri-operat* or peri operat* or perisurg* or peri-surg* or peri surg* or preoperat* or pre-operat* or presurg* or pre-surg*) near/3 (tamoxifen* or aromatase* or AI*)):ti,ab,kw (Word variations have been searched)
#35	#21 and #34
#36	#33 or #35
#37	(initial near/3 (therap* or treatment*)):ti,ab,kw (Word variations have been searched)
#38	(primary near/3 surg*):ti,ab,kw (Word variations have been searched)
#39	#37 or #38
#40	#21 and #32 and #39
#41	(aromatase inhibitor* or anastrazole or arimidex or letrozole or femara or exemestane or aromasin or Nolvadex or tamoxifen*):ti (Word variations have been searched)
#42	(mastectom* or mammectom* or surg*):ti (Word variations have been searched)
#43	#21 and #41 and #42
#44	#36 or #40 or #43

Literature search strategies for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 September 27**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 28 September 2017

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz

#	Searches
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	exp Radiotherapy/ use prmz
34	exp radiotherapy/ use oemezd
35	radiotherapy.fs.
36	(radiotherap$ or radiat$ or irradiat$ or brachytherap$ or tomotherap$).mp.
37	(fractionat$ or hyperfractionat$ or hypofractionat$).mp.
38	33 or 34 or 35 or 36 or 37
39	exp Mastectomy/ use prmz
40	exp mastectomy/ use oemezd
41	(mastectom$ or post?mastectom$ or post-mastectom$ or postmastectom$).mp.
42	(mammectom$ or post?mammectom$ or post-mammectom$ or postmammectom$).mp.
43	39 or 40 or 41 or 42
44	32 and 38 and 43
45	Neoadjuvant Therapy/ use prmz
46	neoadjuvant therapy/ use oemezd
47	neoadjuvant$.tw.
48	(primary adj3 (chemotherap$ or therap$ or treatment$)).tw.
49	(induct$ adj3 (chemotherap$ or therap$ or treatment$)).tw.
50	((perioperat$ or peri-operat$ or peri operat$ or perisurg$ or peri-surg$ or peri surg$ or preoperat$ or pre-operat$ or presurg$ or pre-surg$) adj3 (chemotherap$ or therap$ or treatment$)).tw.
51	or/45-50
52	44 and 51
53	remove duplicates from 52
54	limit 53 to yr="1990 -Current"

Database: Cochrane Library via Wiley Online

Date of last search: 28 September 2017.

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11

#	Searches
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Radiotherapy] explode all trees
#23	(radiotherap* or radiat* or irradiat* or brachytherap* or tomotherap*):ti,ab,kw (Word variations have been searched)
#24	(fractionat* or hyperfractionat* or hypofractionat*):ti,ab,kw (Word variations have been searched)
#25	#22 or #23 or #24
#26	MeSH descriptor: [Mastectomy] explode all trees
#27	(mastectom* or post?mastectom* or post-mastectom* or postmastectom*):ti,ab,kw (Word variations have been searched)
#28	(mammectom* or post?mammectom* or post-mammectom* or postmammectom*):ti,ab,kw (Word variations have been searched)
#29	#26 or #27 or #28
#30	#21 and #25 and #29 Publication Year from 1990 to 2017
#31	MeSH descriptor: [Neoadjuvant Therapy] explode all trees
#32	neoadjuvant*:ti,ab,kw (Word variations have been searched)
#33	((perioperat* or peri-operat* or peri operat* or perisurg* or peri-surg* or peri surg* or preoperat* or pre-operat* or presurg* or pre-surg* or primary or induct*) near/3 (chemotherap* or therap* or treatment*)):ti,ab,kw (Word variations have been searched)
#34	#31 or #32 or #33
#35	#30 and #34

Literature search strategies for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 September 27**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 28 September 2017.

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz

#	Searches
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	Neoadjuvant Therapy/ use prmz
34	neoadjuvant therapy/ use oemezd
35	neoadjuvant$.tw.
36	(primary adj3 (chemotherap$ or therap$ or treatment$)).tw.
37	(induct$ adj3 (chemotherap$ or therap$ or treatment$)).tw.
38	((perioperat$ or peri-operat$ or peri operat$ or perisurg$ or peri-surg$ or peri surg$ or preoperat$ or pre-operat$ or presurg$ or pre-surg$) adj3 (chemotherap$ or therap$ or treatment$)).tw.
39	33 or 34 or 35 or 36 or 37 or 38
40	Cisplatin/ use prmz
41	cisplatin/ use oemezd
42	Carboplatin/ use prmz
43	carboplatin/ use oemezd
44	Platinum/ use prmz
45	Platinum Compounds/ use prmz
46	platinum/ use oemezd
47	platinum derivative/ use oemezd
48	(platin$ or cisplatin$ or platinol$ or carboplatin$ or paraplatin$ or platidiam$).tw.
49	(nsc-119875 or nsc-241240 or cbdca or jm-8).tw.
50	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).tw.
51	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).tw.
52	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53	Triple Negative Breast Neoplasms/ use prmz
54	triple negative breast cancer/ use oemezd
55	((triple or double) adj3 negativ$).tw.
56	TNBC.tw.
57	(basal$ adj (like$ or type$ or subtype$)).tw.
58	(BRCA$ adj (mutat$ or alter$)).tw.
59	55 or 57 or 58
60	32 and 59
61	53 or 54 or 56 or 60
62	32 and 39 and 52
63	32 and 52 and 61
64	62 or 63
65	limit 64 to yr="1995 -Current"
66	remove duplicates from 65
67	Limit 66 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

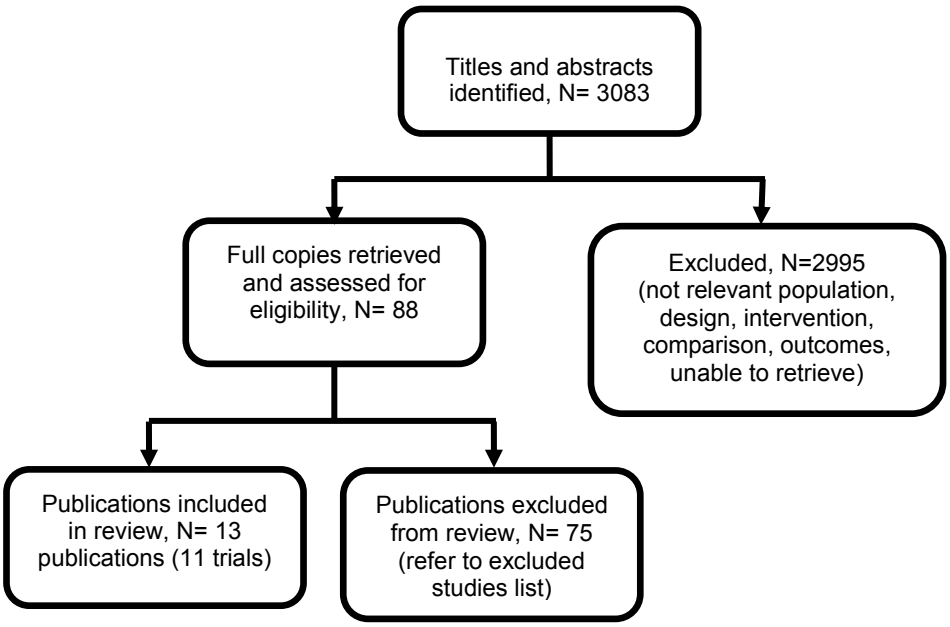
Date of last search: 28 September 2017.

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Cisplatin] explode all trees
#23	MeSH descriptor: [Carboplatin] explode all trees
#24	MeSH descriptor: [Platinum] explode all trees
#25	MeSH descriptor: [Platinum Compounds] explode all trees
#26	(platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*):ti,ab,kw (Word variations have been searched)
#27	(nsc-119875 or nsc-241240 or cbdca or jm-8):ti,ab,kw (Word variations have been searched)
#28	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum):ti,ab,kw (Word variations have been searched)
#29	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum):ti,ab,kw (Word variations have been searched)
#30	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31	#21 and #30 Publication Year from 1995 to 2017

Appendix C – Clinical evidence study selection

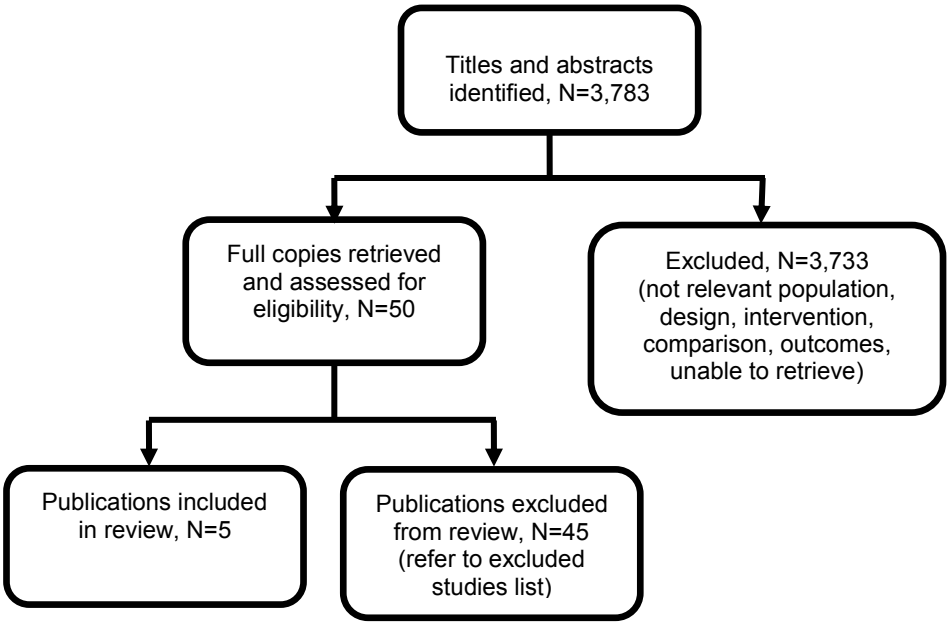
Clinical study selection for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

Figure 1: Flow diagram of clinical article selection for question 10.1: What is the effectiveness of neoadjuvant chemotherapy?



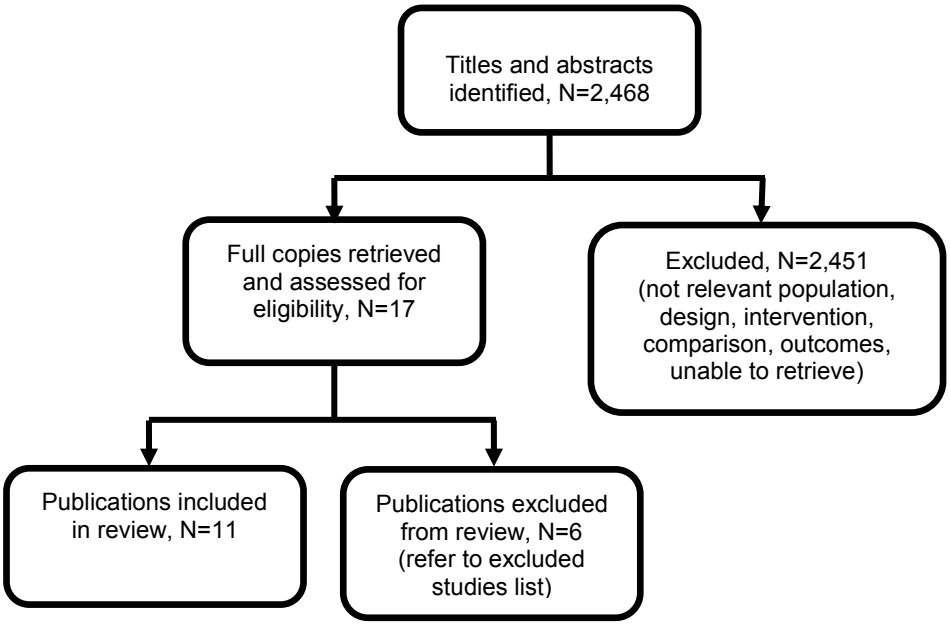
Clinical study selection for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

Figure 2: Flow diagram of clinical article selection for postmastectomy radiotherapy after neoadjuvant chemotherapy



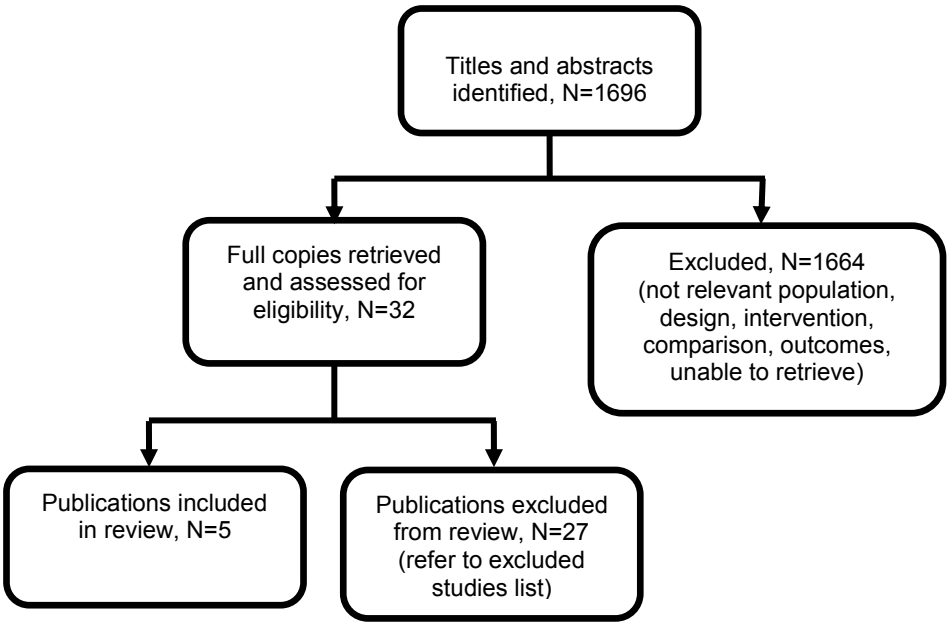
Clinical study selection for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

Figure 3: Flow diagram of clinical article selection for postmastectomy radiotherapy after neoadjuvant chemotherapy



Clinical study selection for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

Figure 4: Flow diagram of clinical article selection for systemic therapy in triple negative or BRCA germ line mutation



Appendix D – Clinical evidence tables

Clinical evidence tables for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

Table 15: Studies included in the review

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Fisher, B., Bryant, J., Wolmark, N., Mamounas, E., Brown, A., Fisher, E. R., Wickerham, D. L., Begovic, M., DeCillis, A., Robidoux, A., Margolese, R. G., Cruz Jr, A. B., Hoehn, J. L., Lees, A. W., Dimitrov, N. V., Bear, H. D., Effect of preoperative chemotherapy on the outcome of women with operable breast cancer, Journal of Clinical Oncology, 16, 2672-2685, 1998 **Ref Id** 655537 **Country/ies where the study was carried out**	**Sample size** N= 1523 (ITT) Neoadjuvant CT, n=763 Adjuvant CT, n=760 **Characteristics** Gender: 100% women **Intervention** / **Control** **Neoadjuvant CT (n=760)** / **Adjuvant CT (n=763)** **Age** **≤49**: 51% / 52% **≥50**: 49% / 48% **50-59**: 25% / 26% **≥60**: 23% / 22% **Mean age (years)**: 50 (sd=11) / 50 (sd=11) **Ethnicity**	**Interventions** **Intervention:** Neoadjuvant anthracycline-based chemotherapy then surgery **Control:** Surgery then adjuvant anthracycline-based chemotherapy	**Details** NSABP B-18 trial. Chemotherapy consisted in 4 x AC every 21 days (doxorubicin [60 mg/m^2] and cyclophosphamide [600 mg/m^2]). Surgery consisted of either breast-conserving surgery (lumpectomy) and axillary lymph node dissection or modified radical mastectomy. Before randomisation, surgeons required to report intended type of surgery independent of effect of CT on staging. After start of CT, patients≥50 years-old received 10 mg oral tamoxifen, twice a day for 5 years. Patients who had breast-conserving	**Results** **Local recurrence:** DFS at 5-year FU: p=0.99 (Neoadjuvant, n=743, events=256; Adjuvant, n=752, events=258) [data from Fisher et al. 1998] DFS at 9-year FU: RR=0.95 (95% CI 0.88-1.1), p=0.5 for comparison of adjuvant vs neoadjuvant (Neoadjuvant, n=742, events=323; Adjuvant, n=751, events=338) [result reported as RR; data from Wolmark et al. 2001]. DFS at 16-year FU: HR=0.93, p=0.27 (Neoadjuvant, n=742, events=410; Adjuvant, n=751, events=434) [data from Rastogi et al. 2008] **pCR:** **BC rate:** OS at 5-year FU: p= 0.83 (Neoadjuvant, n=743, deaths=158; Adjuvant, n=752, deaths=163) [data from Fisher et al. 1998] OS at 9-year FU: RR=1.02 (95% CI 0.84-1.21), p=0.8 for comparison of adjuvant vs neoadjuvant (Neoadjuvant, n=742, deaths=221; Adjuvant, n=751, deaths=218)) [result reported as Risk Ratio, data from Wolmark et al. 2001].	**Selection bias: random sequence generation** Low: used biased-coin minimization algorithm used, stratified by age (≤49, ≥50), clinical tumour size (≤2cm, 2.1-5cm, ≥5.1 cm), clinical nodal status (+/-) and participating institution. **Selection bias: allocation concealment** Unclear: no details provided

Study details	Participants			Interventions	Methods	Outcomes and results	Comments
USA, Canada **Study type** RCT **Aim of the study** To determine if neoadjuvant combined doxorubicin and cyclophosphamide chemotherapy is more effective than adjuvant chemotherapy **Study dates** Recruitment, October 1998-April 1993 **Source of funding** Supported in part by: Public Health Service Grants (No. U10CA-12027, U10CA-69974, U10CA-37377, and U10CA-69651) from National Cancer Institute, Department of Health and Human Services; Astra-Zeneca; Sanofi-Aventis.	**White**	81%	81%		surgery given breast RT **Intervention:** Patients who had breast-conserving surgery given breast RT after recovery from surgery. **Control:** Patients who had breast-conserving surgery given breast RT after recovery from CT.	OS at 16-year FU: HR=0.99, p=0.9 (Neoadjuvant, n=742, deaths=310; Adjuvant, n=751, deaths=315) [data from Rastogi et al. 2008] **Response rate:**	**Selection bias: overall judgement** Unclear **Performance bias** Low: Lack of blinding not likely to affect outcome **Detection bias** Low: Lack of blinding not likely to affect outcome **Attrition bias** Low: missing data not likely related to true outcome. Total dropouts, n=21 (14 in neoadjuvant group, 7 in adjuvant group). Deemed
	Black	9%	11%				
	Other	8%	7%				
	Unknown	2%	1%				
	ER Status						
	0-9	Not available	33%				
	10-99	Not available	38%				
	≥100	Not available	19%				
	Unknown	Not available	10%				
	Inclusion criteria (1) Female patient at participating NSABP institution; (2) primary, palpable, operable breast cancer; (i.e. T1-3, N0-1, M0); (3) diagnosis of BC using fine-needle aspiration or core biopsy; (4) Written informed consent. **Exclusion criteria** (1) Diagnosis of BC using open (incisional or excision) biopsy. **Reported subgroups** Wolmark et al. 2001: Age (data reported); clinical lymph node status, clinical tumour size [no significant effect of interaction of covariates with treatment reported, no data provided].						

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					ineligible after report of first outcome, n=2 (1 in each group). Refused consent, n=2 (1 in each group). Advanced disease at randomisation, n=6 (5 in neoadjuvant group, 1 in adjuvant group). Other reasons (not stated), n=8 (groups not stated). **Selective reporting** Low: All expected outcomes reported **Indirectness** **Limitations** **Other information** Other sources of bias:

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>appears free from other sources of bias.</td></tr>
<tr><td>Full citation

Gianni, L., Baselga, J., Eiermann, W., Porta, V. G., Semiglazov, V., Lluch, A., Zambetti, M., Sabadell, D., Raab, G., Cussac, A. L., Bozhok, A., Martinez-Agullo, A., Greco, M., Byakhov, M., Lopez Lopez, J. J., Mansutti, M., Valagussa, P., Bonadonna, G., Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy, Clinical Cancer Research, 11, 8715-8721, 2005</td><td>Sample size

N=1355

Arm 1: Neoadjuvant doxorubicin + paclitaxel then CMF, followed by surgery, n=451

Arm 2: Surgery then adjuvant doxorubicin + paclitaxel, followed by CMF, n=451

Arm 3: Neoadjuvant doxorubicin then CMF, followed by surgery, n=453

Characteristics

Gender: 100% Women

Ethnicity: NR

<table><tr><th></th><th>Intervention

Neoadjuvant CT

(N=451)</th><th>Control

Adjuvant CT

(n=451)</th></tr><tr><td>Age</td><td></td><td></td></tr><tr><td><50 years-old</td><td>44.9%</td><td>46.8%</td></tr><tr><td>>≥50 years-old</td><td>55.1%</td><td>53.2%</td></tr><tr><td>Hormonal receptor status</td><td></td><td></td></tr><tr><td>ER/PR+</td><td>67.9%</td><td>68.3</td></tr><tr><td>Er/PR-</td><td>31.2%</td><td>30.8</td></tr></table></td><td>Interventions

Intervention: Neoadjuvant anthracyline-based combination chemotherapy then surgery

Control-1: Surgery then combination adjuvant anthracycline-based chemotherapy

Control-2: Surgery then single-agent adjuvant anthracycline-based chemotherapy</td><td>Details

ECTO 2005 trial.

Chemotherapy in intervention and control-1 was 4 x doxorubicin (60 mg/m^2 i.v. bolus) and paclitaxel (200 mg/m^2 infused over 3 hrs) every 3 weeks, then 4 x CMF (i.v. cyclophosphamid [600 mg/m^2], methotrexate [40 mg/m^2], 5-fluororacil [600 mg/m^2]) on days 1 and 8 every 4 weeks. Breast RT (50 Gy after end of CT or, for intervention group, within 4 weeks after surgery) required after breast-conserving surgery; chest wall irradiation. Dose reduction allowed only when febrile neutropenia, or >grade 2</td><td>Results

Local recurrence:

<table><tr><th></th><th>Intervention

Neoadjuvant CT

(n=451)</th><th>Control-1

Adjuvant combo CT

(n=451)</th><th>Control-2

Adjuvant single CT

(n=453)</th></tr><tr><td>Breast-conserving surgery</td><td>5.3%</td><td>5.2%</td><td>6.9%</td></tr><tr><td>Modified radical mastectomy</td><td>2.7%</td><td>3.5%</td><td>2.3%</td></tr></table>DFS: NR

pCR: Neoadjuvant CT arm, 75/438 (breast specimens only); 89/438 (breast specimens + axillary lymph nodes)

BC rate: Intervention, 63% (n=451); Control-1, 33% (n=451) (reported in Gianni et al. 2009)

OS at (data from Gianni et al. 2005)</td><td>Selection bias: random sequence generation

Low: randomised using minimisation algorithm, stratified by primary tumour size (<4 cm, >4 cm), tumour grade (low, intermediate, high), and hormone receptor status (ER and/or PR +/-).

Selection bias: allocation concealment

Low: central allocation

Selection bias:</td></tr>
</table>

Study details	Participants			Interventions	Methods	Outcomes and results	Comments
Ref Id 655665 **Country/ies where the study was carried out** Austria, Czech Republic, Estonia, Germany, Hungary, Italy, Latvia, Poland, Russia, Slovakia, Spain **Study type** RCT **Aim of the study** To evaluate whether addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate and 5-FU improves outcomes when given as neoadjuvant compared to adjuvant chemotherapy. **Study dates** November 1996-May 2002	**Not assessed** 0.9% 0.9 **Tumour grade** **Low** 11.6% 11.6 **Intermediate** 55.1% 54.6 **High** 31.1% 31.2 **Not assessed** 2.2% 2.6 **Inclusion criteria** (1) Female patient at participating institution; (2) >18 years-old; (3) Untreated primary operable breast tumour >2 cm (T2-3, N0-1, M0); (4) known hormone receptor status and tumour grade; (5) Karnofsky PS>70; (6) adequate bone marrow, renal and liver function; (7) normal blood pressure and cardiac function (inc. left ventricular ejection fraction); (8) written informed consent **Exclusion criteria** (1) Locally advanced or bilateral breast carcinoma; (2) prior anticancer treatment; (3) inadequate bone marrow reserve; (4) abnormal renal and liver function tests; (5) history of cardiac disease; (6) pregnancy or lactating; (7) active infection; (8) history of other invasive malignancy; (9) psychiatric disorder prevention informed consent. **Reported subgroups** ER status, PR status and tumour grade for pathologic and clinical complete response.		neuropathyor gastrointestinal toxicity. After surgery/CT, all patients offered 5 consecutive years of tamoxifen (20 mg/day); protocol amended in June 2000 and tamoxifen offered to only ER+ or PR+ women. **Control-2:** Chemotherapy was 4 x doxorubicin (75 mg/m^2 i.v. bolus) every 3 weeks, then 4 x CMF (i.v. cyclophosphamid [600 mg/m^2], methotrexate [40 mg/m^2], 5-fluororacil [600 mg/m^2]) on days 1 and 8 every 4 weeks.	OS at median 76-mo FU (max 126-mo): HR=1.1 (95% CI 0.77-1.59), p=0.6 (Control-1 [n=451] vs Intervention-1 [n=451]) (data from Gianni et al. 2009) Response rate: (Neoadjuvant CT arm only) Complete clinical response, 184 (49%); Partial response, 107 (29%), Minor response, 54 (14%), No response, 25 (7%), Progresive disease, 3 (1%).	**overall judgement** Low **Performance bias** Low: blinding not likely to affect true outcome **Detection bias** Low: blinding not likely to affect true outcome **Attrition bias** Total dropouts, n=31. Intervention, n=3; Control, n=19; arm 3, n=9). Ineligible after randomisation, n=8 (Intervention, n=1; Control, n=5; arm 3, n=2). Refused treatment,

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Grant from Bristol Meyers Squibb					n=23 (Intervention, n=2; Control, n=14; arm 3, n=7). **Selective reporting** Low: all expected outcomes reported **Indirectness** **Limitations** All patients had tumour > 2cm **Other information** No other obvious sources of bias.
Full citation Zhao, C. X., Dong, L., Zhang, J., Yi, R., Influence of neoadjuvant CAF chemotherapy on serum TSGF, CA15-3 and	**Sample size** N=70 Neoadjuvant CT, n=35 Adjuvant CT, n=35 **Characteristics**	**Interventions** **Intervention:** Neoadjuvant anthracycline-based chemotherapy then surgery then	**Details** Chemotherapy consisted in 2 x CAF (i.v. cyclophosphamide [500 mg/m^2] and 5-fluorouracil [500 mg/m^2] on day 1	**Results** Local recurrence: NR DFS: NR pCR: NR BC rate: NR	**Selection bias: random sequence generation** Unclear: no details of

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
CA125 in patients with breast cancer, Journal of International Translational Medicine, 4, 167-171, 2016 **Ref Id** 568181 **Country/ies where the study was carried out** People's Republic of China **Study type** RCT **Aim of the study** To evaluate effect of neoadjuvant chemotherapy on serum tumour specific growth factor, carbohydrate antigen CA15-3 and CA125 in patients with breast cancer **Study dates** January 2013-January 2015 **Source of funding**	Gender: 100% women Median Age: Neoadjuvant CT, 45 years-old (range 32-63); Adjuvant CT, 47 years-old (range 31-65) Ethnicity: NR (plausibly all Chinese) **Intervention** / **Control** **Neoadjuvant CT** / **Adjuvant CT** **(n=35)** / **(n=35)** **Stage IIIa**: 16 / 15 **Stage IIIb**: 19 / 20 **Inclusion criteria** (1) Female patient at Xuzhou Cancer Hospital, Jiangsu, China; (2) advanced invasive breast cancer by clinical examination; (3) written, informed consent. **Exclusion criteria** NR **Reported subgroups** NR	adjuvant anthracycline-based chemotherapy **Control:** Surgery then adjuvant anthracycline-based chemotherapy	and day 8, i.v. doxorubicin [30 mg/m^2] on day 1) every 21 days. Venous blood collected before and after CT. Efficacy evaluated using Response Evaluation Criteria in Solid Tumours (RECIST). **Intervention:** patients also received 2 x CAF after surgery. **Control:** Surgery consisted of radical mastectomy.	OS: NR Response rate: **Intervention** **Neoadjuvant CT** **(n=35)** **Complete remission (response)**: 10 **Partial remission (response)**: 14 **Stable Disease**: 7 **Progressive disease**: 4 **Objective Response Rate (complete + partial)***: 24/35 (68.6%) **Disease control rate (complete + partial + stable)**: 31/35 (88.6%) *Statistically significant difference (p<0.05) bet for Objective response rate	randomisation method. **Selection bias: allocation concealment** Unclear: no details provided **Selection bias: overall judgement** Unclear **Performance bias** Low: outcome not likely to be affected by blinding **Detection bias** Low: outcome not likely to be affected by blinding **Attrition bias** Low: No dropouts reported

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
NR					**Selective reporting** Unclear: no protocol provided, does not report local recurrence, OS or DFS. **Indirectness** All patients had stage IIIa or IIIb advanced invasive breast cancer. **Limitations** Study reports that participants were 'selected' during recruitment period, but no further details provided. **Other information**

Study details	Participants				Interventions	Methods	Outcomes and results	Comments
Full citation Mauriac, L., MacGrogan, G., Avril, A., Durand, M., Floquet, A., Debled, M., Dilhuydy, J. M., Bonichon, F., Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: A unicentre randomized trial with a 124-month median follow-up, Annals of Oncology, 10, 47-52, 1999 **Ref Id** 656024 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study** To determine (i) whether neoadjuvant chemotherapy improves overall	**Sample size** N=272 (PPA) Neoadjuvant CT, N=134 Adjuvant CT, N=138 **Characteristics** Gender: 100% women **Intervention** **Neoadjuvant CT** **EPR-** **(n=61)** **Control** **Adjuvant CT** **EPR +** **(n=73)** **EPR -** **(n=64)** **Mean age (years)** 51.8 53.8 52.2 **Scarf Bloom Richardson Grading from drill-biopsy** **Grade 1** 13 9 3 **Grade 2** 25 47 29 **Grade 3** 17 16 25 **Grade not determined** 6 1 7 Ethnicity: NR Histological subtype: All participants had invasive breast carcinoma. **Inclusion criteria**				**Interventions** **Intervention:** Neoadjuvant chemotherapy then adjusted locoregional treatment. **Control:** Surgery then adjuvant chemotherapy	**Details** Bordeaux 1991 trial, second analysis with median follow up of 124-mo. Both arms received same course of CT consisting of 6 courses, 1 every 3 weeks: first three courses consisted of VEM [epirubicin (50 mg/m^2), vincristine (1 mg/m^2), methotrexate (20 mg/m^2)], second three courses consisted of MTV [mitomycin C (10mg/m^2), thiotepa (20 mg/m^2), vindesine (4 mg/m^2)]. Dose reduction in line with haematologic toxicity. **Intervention:** Neoadjuvant CT within 4 days of core biopsy result. Locoregional treatment in next 21 days dependent on tumour regression (Complete response: RT of	**Results** **Intervention group:** All 134 patients had neoadjuvant CT. Subsequently, 84 (63.1%) had breast conserving surgery, 44 (33%) had RT only, 40 (30%) had both breast-conserving surgery and RT, and 49 (36.9%) had mastectomy. **Control group:** Reports 136 patients had modified radical mastectomy, with 104 (76%) patients receiving subsequent adjuvant CT. Local recurrence: Intervention 31/134, Control 12/138 DFS: NR pCR: NR BC rate: Intervention 84/134 (Clinical complete response + partial complete response), Control 0/138 OS: data not reported, Kaplan-Meier curve shows no significant difference between arms. (Was significant difference favouring intervention arm at first analysis in 1991). Response rate: (data for intervention arm only) Clinical complete response 44/134, Clinical partial response 40/134, Overall response 84/134.	**Selection bias: random sequence generation** Unclear: no details of randomisation method used. **Selection bias: allocation concealment** Unclear: no details provided. **Selection bias: overall judgement** Unclear **Performance bias** Low: outcome not likely to be influenced by blinding. **Detection bias** Low: outcome not

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
survival compared to adjuvant chemotherapy, and (ii) the factors that predict overall survival and response to neoadjuvant chemotherapy. **Study dates** January 1985-April 1989 **Source of funding** NR	(1) Adult women with operable breast cancer with or without nodal involvement (i.e. T2>3cm or T3 N0-1 M0); (2) Oral informed consent. **Exclusion criteria** (1) Women with T4, N2-3 tumours; (2) Metastatic disease. **Reported subgroups** Oestrogen and progesterone receptor status (EPR)		breast and nodal areas; Partial response: breast-conserving surgery + RT of breast if residual tumour <2cm; modified radical mastectomy without RT if residual tumour >2 cm). No further adjuvant CT if pathologically-proven axillary nodal involvement. **Control:** Initial surgery consisted of modified radical mastectomy if pathologically-proven nodal involvement or absence of both oestrogen and progesterone receptors (EPR-). Adjuvant CT started within 15 days of surgery. No RT allowed.		likely to be influenced by blinding. **Attrition bias** Unclear: Two patients unaccounted for in description of initial treatment for control group **Selective reporting** Unclear: insufficient information provided **Indirectness** **Limitations** Patients in intervention arm received different treatments after neoadjuvant CT depending on response.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					Other information No other obvious sources of bias.
Full citation Broet, P., Scholl, S. M., De la Rochefordiere, A., Fourquet, A., Moreau, T., De Rycke, Y., Asselain, B., Pouillart, P., Short and long-term effects on survival in breast cancer patients treated by primary chemotherapy: An updated analysis of a randomized trial, Breast Cancer Research and Treatment, 58, 151-156, 1999 **Ref Id** 656261 **Country/ies where the study was carried out** France	**Sample size** N=414 (ITT) N=390 evaluable patients Neoadjuvant chemotherapy, n=200 Adjuvant chemotherapy, n=190 **Characteristics** Gender: 100% women Mean Age: 45 years Ethnicity: NR **Inclusion criteria** (1) women only; (2) premenopausal; (3) M0 operable breast tumour; (4) largest tumour 3-7 cm; (5) axillary lymph nodes not clinically involved or involved but not adherent; (6) no prior cancer; (7) no serious concomitant illness. **Exclusion criteria** (1) Bilateral, inflammatory or locally advanced BC **Reported subgroups**	**Interventions** **Intervention:** Neoadjuvant chemotherapy then locoregional treatment (RT ± Surgery) **Control:** RT ± surgery then Adjuvant chemotherapy	**Details** Institut Curie 1994 S-6 trial. Chemotherapy consisted of 4 x FAC (5-fluorouracil [2000 mg/m^2], doxorubicin [50 mg/m^2], i.v. cyclophosphamide [800 mg/m^2]). All patients received RT (mean dose 54 Gy to breast over 6 weeks) using cobolt-60 unit (54 Gy axillary nodes then 10-15 Gy inferior axilla in N1 patients who did not have surgery, and 45 Gy to supraclavicular nodes and internal mammary chain). Surgery only if incomplete response (RT and according to incomplete	**Results** Median FU (months)=105 (range 27-135). **Local recurrence: Intervention 49/200, 37/190 (from Mieog et al. 2007)** **DFS: Intervention 82/200, Control 86/190 (from Mieog et al. 2007)** pCR: NR BC rate: Intervention 164/200, Control 146/190 (from Scholl et al. 1994) OS at 10-yrs: 127 deaths at time of analysis, log rank test p=0.24 (proportional hazards assumption violated). 10-year survival rates: Neoadjuvant CT, 64.6% (71.4-83.4); Adjuvant CT, 60.2% (52.6-68.9). Response rate: Objective RR (>50% regression) Intervention 124/191 (65%), Control 161/190 (85%) (from Scholl et al. 1994)	**Selection bias: random sequence generation** Unclear: no details of randomisation method provided **Selection bias: allocation concealment** Unclear: no details of allocation concealment provided **Selection bias: overall judgement** Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study type RCT **Aim of the study** To evaluate short- and long-term effects of neoadjuvant chemotherapy compared to adjuvant chemotherapy. **Study dates** October 1986-June 1990 **Source of funding** Main author supported by fellowship from Association pour la Rechereche contre le Cancer.			response after RT; wide surgical resection if possible, otherwise mastectomy (e.g. for those with minimal or no response). Patients regularly monitored on regular basis by oncologist or referring physician after randomisation. FU <6mo intervals for first 5 years, then annually. Intervention: CT started after completion of initial assessment. Local regional treatment according to residual tumour amount after CT. Control: CT started within 2 weeks of ending local regional treatment.		**Performance bias** Low risk: outcomes not likely to be influenced by lack of blinding **Detection bias** Unclear: no details of outcome assessment provided **Attrition bias** Unclear: 24 patients dropped out post-randomisation, no details provided (info from Mieog et al. 2007). **Selective reporting** Low: Other outcomes reported in previous articles

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					Indirectness **Limitations** Patients had RT with or without surgery depending on response. **Other information** No other obvious sources of bias.
Full citation Danforth Jr, D. N., Cowan, K., Altemus, R., Merino, M., Chow, C., Berman, A., Chaudhry, U., Shriver, C., Steinberg, S. M., Zujewski, J., Preoperative FLAC/granulocyte-colony-stimulating factor chemotherapy for stage II breast cancer: A prospective	**Sample size** N=53 (ITT) Neoadjuvant CT, n=26 Adjuvant CT, n=27 **Characteristics** Gender: 100% women Age (median, years): Neoadjuvant CT arm: 49 (range 32-68); Adjuvant CT arm: 43 (range 28-66) Ethnicity: NR **Intervention Control**	**Interventions** **Intervention:** Neoadjuvant anthracycline-based chemotherapy then surgery **Control:** Surgery then adjuvant anthracycline-based chemotherapy	**Details** Chemotherapy consisted in 5 x FLAC/GM- or G-CSF every 21 days (i.v. bolus: day 1: cyclophosphamide [600mg/m^2]; days 1, 2 and 3: 5-fluororacil [400 mg/m^2], leucovorin calcium [500 mg/m^2], doxorubicin [15 mg/m^2]). Subcutaneous granulocyte-macrophage	**Results** Fifty-one patients completed 5 cycles of CT. Local recurrence: Intervention 3/26, Control 2/27 DFS at median 9-years FU: p=0.23 (# patients with disease recurrence in intervention vs control: 9/26 vs 11/27) pCR: (Intervention arm only) 2/10 BC rate: Intervention 11/26, Control 11/27 OS at median 9-years FU: p=0.24 (# patients dead in intervention vs control: 3/26 vs 6/27) Response rate: (data for neoadjuvant arm only; 9 patients not assessable due to	**Selection bias: random sequence generation** Unclear: no details of randomisation method **Selection bias: allocation concealment**

Study details	Participants			Interventions	Methods	Outcomes and results	Comments
randomized trial, Annals of surgical oncology, 10, 635-644, 2003 **Ref Id** 621139 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To determine if intensive neoadjuvant chemotherapy reduces locoregional tumours in women with stage II breast cancer **Study dates** 1990-November 1998, closed to FU in 2002. **Source of funding** NR		**Neoadjuvant CT** **(N=26)**	**Adjuvant CT** **(N=27)**		colony-stimulating-factor (GM-SCF) 10µg/kg on days 4-16 for first 27 patients; remaining patients received granulocyte-colony-stimulating-factor (G-CSF) 5 µg/kg on days 4-18. Mesna (prophylaxis for cyclophosphamide) administered 15 min before and 4-6 hrs after cyclophosphamide. Dose escalation permitted according to white blood cell count and/or response. Intervention: Treatment after neoadjuvant CT consisted of modified radical mastectomy, axillary dissection, and breast RT, followed by tamoxifen for 5 years. If disease progression after 2 cycles then locoregional therapy; complete response after 4 or less cycles, or no assessable disease at start of CT,	excisional biopsy before CT and clinically negative axilla) Clinical complete response 11/17, clinical partial response 2/17. Objective response rate 13/17 (76.5%); objective response rate for primary tumouronly: 8/10	Low: central randomisation office used **Selection bias: overall judgement** Low **Performance bias** Low: blinding unlikely to affect outcome **Detection bias** Low: blinding unlikely to affect outcome **Attrition bias** Low: ITT analysis. One patient stopped CT after 2 cycles due to adverse effects; 1 patient refused CT
	Histology						
	Invasive ductal carcinoma	21	25				
	Invasive lobular carcinoma	4	2				
	Poorly differentiated	1	0				
	Oestrogen receptor status						
	+	16	16				
	-	9	11				
	Unknown	1	0				
	Inclusion criteria (1) Women only; (2) untreated Stage II BC (i.e. T1-2, N0-1 [AJCC 1989]); (3) histologically-confirmed invasive breast cancer of epithelian origin (patients with bilateral BC eligible only if at least one invasive tumour and most advanced cancer at least clinical stage II; (4) leukocyte count >4000/mm^3; (5) platelet count >100,000/mm^3; (6) liver chemistries (AST, ALT, alkaline phosphatase, total bilirubin) < 1.5 times normal upper limits; (7) creatinine <1.7 mL/min and/or creatinine clearance >45 mL/min; (8) absence of chronic cardiac or pulmonary disease; (9) Written informed consent. **Exclusion criteria** Patients (1) with excisional biopsy followed by subsequent treatment; or (2) with history of malignant neoplasms except for those who have had (i) (pre-1997) curatively-						

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	treated basal cell carcinoma of skin, (ii) (pre-1997) surgically-excised carcinoma of cervix in situ, or (iii) (post-1997 only) curative therapy of non-breast malignancy and no evidence of recurrence after 10 or more years; (3) who are pregnant. **Reported subgroups** Axillary lymph node metastases		completed all 5 cycles. Control: Surgery consisted of modified radical mastectomy or axillary dissection. Patients received breast RT after CT, followed by 10 mg/twice a day of tamoxifen for 5 years.		post-randomisation. **Selective reporting** Unclear: insufficient detail **Indirectness** Patients had combination hormonal therapy **Limitations** Does escalation permitted depending on white blood cell count/adverse events; protocol amended in 1997 to use G-CSF rather than GM-CSF. **Other information** No other obvious sources of bias.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Deo, S. V. S., Bhutani, M., Shukla, N. K., Raina, V., Rath, G. K., Purkayasth, J., Randomized Trial Comparing Neo-Adjuvant Versus Adjuvant Chemotherapy in Operable Locally Advanced Breast Cancer (T4b N0-2 MO), Journal of Surgical Oncology, 84, 192-197, 2003 **Ref Id** 656329 **Country/ies where the study was carried out** India **Study type** RCT **Aim of the study** To evaluate whether neoadjuvant chemotherapy provides survival	**Sample size** N=101 (ITT) Neoadjuvant CT, n=50 Adjuvant CT, n=51 **Characteristics** Gender: 100% women Median Age: Neoadjuvant CT, 50 years-old (range 26-68); Adjuvant CT, 48 years-old (range 22-72). Ethnicity: NR (presumably all Indian) ~75% of sample had tumours >5cm at randomisation. **Inclusion criteria** (1) Untreated female patients with bidimensionally palpable and measurable primary operable breast cancer (i.e. T4b, N0-2, M0; AJCC TNM, 6th ed.); (2) diagnosis by fine-needle aspiration cytology; (3) adequate organ function (leukocyte count>4000 mm^3; haemoglobin>9.5 g/dL; aspartate aminotransferase and alanine aminotransferase<100 IU/ml; serum creatinine<1.2 mg/dl; creatinine clearance>60 ml/min); (4) informed consent. **Exclusion criteria** (1) ECOG performance stats III or IV; (2) inoperable locally advanced disease (extensive edema of breast and arm, or axillary lymph nodes fixed to underlying structures); (3) inflammatory BC; (4) evidence of metastases; (5) pregnancy; (6) patients with left ventricular ejection fraction<50% if radionuclide scan clinically indicated. **Reported subgroups**	**Interventions** **Intervention:** Neoadjuvant anthracycline-based chemotherapy then surgery, then adjuvant anthracycline-based chemotherapy **Control:** Surgery then adjuvant anthracycline-based chemotherapy	**Details** Chemotherapy consisted of CEF (i.v. cyclophosphamide [500 mg/m^2], epirubicin [50 mg/m^2], 5-flurouracil [500 mg/m^2]) on days 1 and 5 by short infusion every four weeks. Dose reduction or delay permitted according to standard guidelines. All patients received 50 Gy over 5 weeks using conventional fractionation (2 Gy/no./day) of external beam RT over 5 weeks to chest wall, ipsilateral internal mammary, supraclavicular and axillary lymphnodes using Cobalt machine within 4 weeks after scheduled CT. Follow up every 3 months.	**Results** Local recurrence: Intervention, 2/50; Control, 4/51. DFS at median 25-mo FU: log rank p=0.18 (DFS rate: Intervention, 61%; Control, 76%) pCR for tumours: (intervention arm only) 2/7 (i.e. 2 of 7 patients who had complete clinical response to neoadjuvant CT). BC rate: NR OS at median 25-mo FU: log rank p=0.42 (OS rate: Intervention, 76%; Control, 82%). Response rate for tumours: (Intervention arm only) Complete response, 7/50; Partial response, 26/50; Stable disease, 15/50; Progressive disease, 2/50. Objective response rate, 33/50. Response rate for axillary nodes: (Intervention arm only) Complete response, 24/50; Partial response, 15/50; Stable disease, 0/50; Progressive disease, 2/50. **Intervention** **Neoadjuvant CT** **(n=50)** / **Control** **Adjuvant CT** **(n=51)** **Distant relapse** 13 / 7	**Selection bias: random sequence generation** Low: used computerised log (presumably random number table). **Selection bias: allocation concealment** Unclear: no details provided **Selection bias: overall judgement** Unclear **Performance bias** Low: outcome not likely to be affected by blinding.

Study details	Participants	Interventions	Methods	Outcomes and results			Comments
advantage compared to adjuvant chemotherapy in operable locally advanced breast cancer. **Study dates** January 1997-August 2001 **Source of funding** NR	Pathological nodal status		**Intervention:** CT consisted of 3 x CEF before surgery, and 3 x CEF after surgery, and started after initial assessment. **Control:** Surgery consisted of (i) modified radical mastectomy (default treatment) or (ii) radical mastectomy for patients found to have invasion of pectoral fascia or muscle at surgery. Latissimus dorsi or transverses abdominus myocutaneous flap repair performed in patients in whom primary closure following mastectomy could not be achieved. Complete axillary clearance (inc. level I, II and III) performed in all patients. CT consisted of 6 x CEF after surgery, and started within 2 weeks of surgery.	**Dead with disease** **Dead - other causes** **Alive event free**	11 1 34	9 0 40	**Detection bias** Low: outcome not likely to be affected by blinding. **Attrition bias** Low: No dropouts reported **Selective reporting** Unclear: insufficient detail **Indirectness** All patients had locally advanced T4b, N0-2 breast cancer. **Limitations** All patients had locally advanced T4b, N0-2 breast cancer.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					Other information
Full citation Gianni, L., Baselga, J., Eiermann, W., Porta, V. G., Semiglazov, V., Lluch, A., Zambetti, M., Sabadell, D., Raab, G., Cussac, A. L., Bozhok, A., Martinez-Agullo, A., Greco, M., Byakhov, M., Lopez, J. J. L., Mansutti, M., Valagussa, P., Bonadonna, G., Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European cooperative trial in operable breast cancer, Journal of Clinical Oncology,	**Sample size** **Characteristics** ECTO 2005 trial, follow-up results to Gianni et al. 2005. See Gianni et al. 2005 for more details. **Inclusion criteria** **Exclusion criteria** **Reported subgroups**	**Interventions** ECTO 2005 trial, follow-up results to Gianni et al. 2005. See Gianni et al. 2005 for more details.	**Details** ECTO 2005 trial, follow-up results to Gianni et al. 2005. See Gianni et al. 2005 for more details.	**Results** ECTO 2005 trial, follow-up results to Gianni et al. 2005. See Gianni et al. 2005 for more details.	**Selection bias: random sequence generation** **Selection bias: allocation concealment** **Selection bias: overall judgement** **Performance bias** **Detection bias** **Attrition bias** **Selective reporting** **Indirectness** **Limitations** ECTO 2005 trial, follow-up results to

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
27, 2474-2481, 2009 **Ref Id** 615879 **Country/ies where the study was carried out** Austria, Czech Republic, Estonia, Germany, Hungary, Italy, Latvia, Poland, Russia, Slovakia, Spain **Study type** RCT **Aim of the study** ECTO 2005 trial, follow-up results to Gianni et al. 2005. See Gianni et al. 2005 for more details. **Study dates** **Source of funding**					Gianni et al. 2005. See Gianni et al. 2005 for more details. **Other information**
Full citation Mieog, J. S. D., Van Der Hage, J. A., Van De Velde,	**Sample size** Nine studies are included from this review: • Bordeaux 1991 (Mauriac et al. 1999), N=272	**Interventions** Intervention 1: Neoadjuvant anthracycline-	**Details** **Neoadjuvant CT (Arm 1) vs**	**Results:** see Forest plots	**Selection bias: random**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
C. J. H., Preoperative chemotherapy for women with operable breast cancer, Cochrane Database of Systematic Reviews, (2) (no pagination), 2007 **Ref Id** 538490 **Country/ies where the study was carried out** Various **Study type** Systematic review/Meta-analysis **Aim of the study** To determine effectiveness of neoadjuvant chemotherapy compared to adjuvant chemotherapy in women with M0 breast cancer **Study dates** Until August 4, 2005	• EORTC 2001 study (van der Hage et al. 2001), N=698 • Institut Curie 1994 study (Broet et al. 1999), N=414 • NSABP 1998 study (Fisher et al. 1998; Wolmark et al. 2001), N=1523 • Royal Marsden 1998 study (Cleator et al. 2005; Makris et al. 1998), N=309 • USA 2003 study (Danforth et al. 2003), N=53 histologically confirmed stage II BC (T1N1, T2N0, T2N1) • Institute Curie 1991 (Scholl 1991) N=196 • ECTO 2005 (Gianni 2005) N=272 • Japan 1998 (Enomoto 1998) N=50 **Characteristics** The following studies that examine anthracycline-based chemotherapy regimens are included in this review. Bordeaux 1991 study (Mauriac et al. 1999) EORTC 2001 study (van der Hage et al. 2001) Institut Curie 1994 study (Broet et al. 1999) NSABP 1998 study (Fisher et al. 1998; Wolmark et al. 2001) Royal Marsden 1998 study (Cleator et al. 2005; Makris et al. 1998) USA 2003 study (Danforth et al. 2003): Median age: Arm 1=49, Arm 2=42. Range: 28-68; Premenopausal=60%; T1=4%, T2=96%. Clinical lymph node involvement=28% . The following studies are excluded because they examine non-anthracycline-based chemotherapy regimens or are conference abstracts: Eiermann 2003 (conference abstract)	based chemotherapy ; Control 1: Adjuvant anthracycline-based chemotherapy . Intervention 2: Neoadjuvant anthracycline-based chemotherapy + adjuvant anthracycline-based chemotherapy ; Control 2: Adjuvant anthracycline-based chemotherapy .	**Adjuvant CT (Arm 2) (8 articles)** **Bordeaux 1991 study** (Mauriac et al. 1999) Arm 1: 3 x EVM + 3 x MTV, then (i) Radiotherapy if complete response, (ii) Radiotherapy + breast-conserving therapy if partial response, otherwise (iii) mastectomy. Arm 2: Mastectomy then ±3 x EVM + 3 x MTV. **EORTC 2001 study** (van der Hage et al. 2001) Arm 1: 4 x FEC then surgery. Arm 2: Surgery then 4 x FEC. **Institut Curie 1994 study** (Broet et al. 1999) Arm 1: 2 x FAC, +2 x FAC if responder, then radiotherapy + surgery. Arm 2: Radiotherapy + surgery then 4 x FAC.		**sequence generation** **Selection bias: allocation concealment** **Selection bias: overall judgement** **Performance bias** **Detection bias** **Attrition bias** **Selective reporting** **Indirectness** **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Cochrane Organisation	Forouhi 1995 (non-anthracycline-based CT study) Gazet 2001 (non-anthracycline-based CT study) Gianni 2005 (conference abstract) Jakesz 2001 (conference abstract) Ostapenko 1998 (conference abstract) Semiglazov 1994 (non-anthracycline-based CT study) **Inclusion criteria** Women only; TNM stage T1c, T2, T3, N0 to 2, and M0 (AJCC stage I-IIIA);RCT that compares (1) neoadjuvant with adjuvant chemotherapy, or (2) neoadjuvant + adjuvant chemotherapy with adjuvant chemotherapy, where chemotherapy agents are (i) those that damage DNA template, (ii) spindle poisons, or (iii) antimetabolites; studies report overall survival, disease-free survival, locoregional recurrence as first event (primary outcomes), or tumour response rate, association with pathological complete response with clinical outcome, type of locoregional treatment, changes of originally planned locoregional treatment, adverse effects or quality of life (secondary outcomes). **Exclusion criteria** No restrictions on age or menopausal status. **Reported subgroups** Type of local treatment; Type of treatment arm; Type of chemotherapy; Methodological quality; Outliers		**NSABP 1998 study** (Fisher et al. 1998; Wolmark et al. 2001) Arm 1: 4 x AC then surgery. Arm 2: Surgery then 4 x AC. **USA 2003 study** (Danforth et al. 2003) Arm 1: 5 x FLAC/G-CSF then surgery. Arm 2: Surgery then 5 x FLAC/G-CSF. **Neoadjuvant CT + Adjuvant CT (Arm 1) vs Adjuvant CT (Arm 2) (1 trial, 2 articles)** **Royal Marsden 1998 study** (Cleator et al. 2005; Makris et al. 1998) Arm 1: 4 x (M)MM + TAM then surgery ± radiotherapy, then 4 x (M)MM. Arm 2: Surgery ±		

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
			radiotherapy, then 8 x (M)MM + TAM.		
Full citation Rastogi, P., Anderson, S. J., Bear, H. D., Geyer, C. E., Kahlenberg, M. S., Robidoux, A., Margolese, R. G., Hoehn, J. L., Vogel, V. G., Dakhil, S. R., Tamkus, D., King, K. M., Pajon, E. R., Wright, M. J., Robert, J., Paik, S., Mamounas, E. P., Wolmark, N., Preoperative chemotherapy: Updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27, Journal of clinical oncology, 26, 778-785, 2008 **Ref Id** 572132 **Country/ies where the study was carried out**	**Sample size** **Characteristics** NSABP B-18 trial, follow-up results of Fisher et al. 1998. See Fisher et al. 1998 for more details. **Inclusion criteria** **Exclusion criteria** **Reported subgroups**	**Interventions** NSABP B-18 trial, follow-up results of Fisher et al. 1998. See Fisher et al. 1998 for more details.	**Details** NSABP B-18 trial, follow-up results of Fisher et al. 1998. See Fisher et al. 1998 for more details.	**Results** NSABP B-18 trial, follow-up results of Fisher et al. 1998. See Fisher et al. 1998 for more details.	**Selection bias: random sequence generation** **Selection bias: allocation concealment** **Selection bias: overall judgement** **Performance bias** **Detection bias** **Attrition bias** **Selective reporting** **Indirectness** **Limitations** NSABP B-18 trial,

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
USA, Canada **Study type** RCT **Aim of the study** NSABP B-18 trial, follow-up results of Fisher et al. 1998. See Fisher et al. 1998 for more details. **Study dates** **Source of funding**					follow-up results of Fisher et al. 1998. See Fisher et al. 1998 for more details. **Other information**
Full citation Van der Hage, J. A., Van de Velde, C. J. H., Julien, J. P., Tubiana-Hulin, M., Vandervelden, C., Duchateau, L., Preoperative chemotherapy in primary operable breast cancer: Results from the European Organization for Research and Treatment of Cancer Trial 10902, Journal of Clinical Oncology,	**Sample size** N=698 (ITT) Neoadjuvant CT, n=350 Adjuvant CT, n=348 **Characteristics** Gender: 100% women Ethnicity: NR (from van Nes et al. 2009) **Age**	**Intervention** **Neoadjuvant CT (n=350)**	**Control** **Adjuvant CT (N=348)**	**Interventions** **Intervention:** Neoadjuvant anthracycline-based chemotherapy then surgery **Control:** Surgery then adjuvant anthracycline-based chemotherapy	**Details** EORTC 10902 trial. Chemotherapy consisted in 4 x FEC (5-fluorouracil [600 mg/m2], epirubicin [60 mg/m2], and cyclophosphamide [600 mg/m2]) every 3 weeks. CT delayed for maximum of 2 weeks if any haematologic, hepatic, renal or gastrointestinal toxicities on day 1	**Results** Additional RT: Intervention, 237/350; Control, 215/348 Additional hormonal therapy: Intervention, 139/350; Control, 134/348. Treatment modification due to treatment-related febrile neutropenia: Intervention, 38 patients; Control, 44. Time to local recurrence at 4 years: HR=1.13 (0.7-1.81), p=0.61 (Neoadjuvant vs adjuvant) (data from van der Hage et al. 2001) Time to local recurrence at 10 years: HR=1.16 (0.77-1.74), p=0.48 (Neoadjuvant vs adjuvant) (data from Van Nes et al. 2009)	**Selection bias: random sequence generation** Unclear: no details provided. Stratified by institution, age (≤50, >50 years-old), clinical tumour size, clinical node status (N+/-), planned type of surgery.

Study details	Participants			Interventions	Methods	Outcomes and results	Comments
19, 4224-4237, 2001 **Ref Id** 656701 **Country/ies where the study was carried out** Egypt, Greece, Netherlands, France, Poland, Russia, Saudi Arabia, Slovenia, South Africa, Spain, Switzerland, Yugoslovia. **Study type** RCT **Aim of the study** To evaluate efficacy of neoadjuvant compared to adjuvant chemotherapy on (i) survival outcomes, (ii) breast conservation rate, and (iii) locoregional control. **Study dates**	**#≤50 years-old**	192	193		of any cycle. Dose modifications permitted in line with EORTC Breast Cancer Cooperative Group guidelines. All patients who had breast-conserving surgery received whole breast RT. Patients≥50 years-old given 20 mg tamoxifen/day for at least 2 years. **Intervention:** Surgery performed within 4 weeks of end of CT. All patients had adjuvant RT after surgery. **Control:** CT given within 36 hours of surgery. Adjuvant RT after completion of CT course.	Local recurrence: Intervention, 36/350; Control, 33/348. DFS at 4 years: HR=1.15 (0.89-1.48), p=0.27 (Neoadjuvant vs adjuvant) (data from van der Hage et al. 2001, reported as progression-free survival) DFS at 10 years: 1.12 (0.9-1.39), p=0.3 (data from Van Nes et al. 2009) **pCR: to check!** BC rate: Intervention, 122/350 (with RT, n=111; without RT, n=11); Control, 77/348 (with RT, n=71; without RT, n=6) OS at 4 years: HR=1.16 (0.83-1.63), p=0.27 (Neoadjuvant vs adjuvant) (data from van der Hage et al. 2001) OS at 10 years: HR=1.09 (0.83-1.42), p=0.54 (data from Van Nes et al. 2009) Response rate: (Intervention arm only) Complete response, 23/350; Partial response, 148/350; No response, 139/350; Disease progression, 5/350; Not assessable, 16/350; Did not receive CT, 19/350 (ineligible, n=6; refused CT, n=10; adjuvant CT, n=19/350)	**Selection bias: allocation concealment** Low: central allocation **Selection bias: overall judgement** Unclear **Performance bias** Low: not likely outcomes affected by blinding **Detection bias** Low: not likely outcomes affected by blinding **Attrition bias** Low: ITT analysis. 21 patients were ineligible after
	#≥50 years-old	158	155				
	ER status						
	ER+	159	178				
	ER-	60	81				
	Unknown	131	89				
	Planned surgery						
	Mastectomy	268	268				
	Breast-conserving	77	74				
	None	5	6				
	Inclusion criteria (1) Female patient at participating institution; (2) primary operable breast cancer (T1c-T4b), N0-1, M0); (3) core-needle biopsy for either diagnosis of T1c tumours or doubt.suspicion of carcinoma in-situ after fine-needle aspiration; and (4) informed consent. **Exclusion criteria** (1) Aged 70 years or more; (2)bilateral BC; (3) previous BC treatment; (4) presence distant metastases; (5) pregnancy or lactation at diagnosis; (6) previous/current other malignancies except adequately-treated skin or cervix uteri basal or squamous carcinoma; (7) active cardiac disease; (8) WHO performance status >2; or (9) severe haematologic, renal or hepatic abnormalities. **Reported subgroups**						

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
April 1991-May 1999 **Source of funding** Supported by educational grant from Pharmacia & Upjohn, Peapacj, NJ, USA; personal grant from Dutch Cancer Society NKB/KWF, Amsterdam, Netherlands.	Nodal status, menopausal status				randomisation due to (i) ineligible staging (n=17), (ii) WHO performance status>2 (n=3), or >70 years-old (n=1). Did not receive CT (n=40; refused, n=8; post-operative complications, n=2 [both in adjuvant group]; unknown, n=7; no information on treatment/FY, n=7) **Selective reporting** Low: all expected outcomes reported **Indirectness** **Limitations** Radiation protocols

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					varied by institution; dose modification allowed. **Other information** Participating sites consisted of 17 institutions in 14 countries (article only lists 11 countries). Mismatch in baseline data reported in this and van Nes et al. 2009. No other obvious sources of bias.
Full citation Van Nes, J. G. H., Putter, H., Julien, J. P., Tubiana-Hulin, M., Van De Vijver, M., Bogaerts, J., De Vos, M., Van De	**Sample size** **Characteristics** EORTC 10902 trial, follow up of van der Hage et al. 2001. See van der Hage et al. 2001 for more details. **Inclusion criteria**	**Interventions** EORTC 10902 trial, follow up of van der Hage et al. 2001. See van der Hage et al.	**Details** EORTC 10902 trial, follow up of van der Hage et al. 2001. See van der Hage et al. 2001 for more details.	**Results** EORTC 10902 trial, follow up of van der Hage et al. 2001. See van der Hage et al. 2001 for more details.	**Selection bias: random sequence generation** **Selection bias: allocation**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Velde, C. J. H., Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up; Clinical and translational results from the EORTC trial 10902, Breast Cancer Research and Treatment, 115, 101-113, 2009 **Ref Id** 551629 **Country/ies where the study was carried out** Belgium, Netherlands, France **Study type** RCT **Aim of the study** EORTC 10902 trial, follow up of van der Hage et al. 2001. See van der Hage et al. 2001 for more details.	**Exclusion criteria** **Reported subgroups**	2001 for more details.			**concealment** **Selection bias: overall judgement** **Performance bias** **Detection bias** **Attrition bias** **Selective reporting** **Indirectness** **Limitations** EORTC 10902 trial, follow up of van der Hage et al. 2001. See van der Hage et al. 2001 for more details. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates **Source of funding**					
Full citation Wolmark, N., Wang, J., Mamounas, E., Bryant, J., Fisher, B., Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18, Journal of the National Cancer Institute, Monographs., 96-102, 2001 **Ref Id** 581261 **Country/ies where the study was carried out** USA, Canada **Study type** RCT	**Sample size** **Characteristics** NSABP B-18 trial, follow up to Fisher et al. 1998. See Fisher et al. 1998 for more details. **Inclusion criteria** **Exclusion criteria** **Reported subgroups**	**Interventions** NSABP B-18 trial, follow up to Fisher et al. 1998. See Fisher et al. 1998 for more details.	**Details** NSABP B-18 trial, follow up to Fisher et al. 1998. See Fisher et al. 1998 for more details.	**Results** NSABP B-18 trial, follow up to Fisher et al. 1998. See Fisher et al. 1998 for more details.	**Selection bias: random sequence generation** **Selection bias: allocation concealment** **Selection bias: overall judgement** **Performance bias** **Detection bias** **Attrition bias** **Selective reporting** **Indirectness** **Limitations** NSABP B-18 trial,

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study NSABP B-18 trial, follow up to Fisher et al. 1998. See Fisher et al. 1998 for more details. **Study dates** **Source of funding**					follow up to Fisher et al. 1998. See Fisher et al. 1998 for more details. **Other information**

AC, doxorubicin, cyclophosphamide; BC, breast cancer; CAF, cyclophosphamide, doxorubicin, fluorouracil; CEF, cyclophosphamide, epirubicin, fluorouracil; CMF, cyclophosphamide, methotrexate, fluorouracil; CT, chemotherapy; DFS, disease-free survival; DNA, deoxyribonucleic acid; ECTO, European Cooperative Trial in Operable Breast Cancer; EORTC, European Organisation for Research and Treatment of Cancer; EPR, oestrogen and progesterone receptor; ER, oestrogen receptor; EVM, epirubicin, vincristine, methotrexate; FAC, fluorouracil, doxorubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; FLAC, fluorouracil, leucovorin, doxorubicin, cyclophosphamide; FU, follow-up; GM-SCF, granulocyte-macrophage colony-stimulating-factor; Gy, gray; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ITT, intention to treat; IV, intravenous; (M)MM, (mitomycin), methotrexate, mitoxantrone; MTV, mitomycin, thiotepa, vindesine; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; pCR, pathologic complete response; PR, progesterone receptor; RCT, randomised controlled trials; RECIST, Response evaluation criteria in solid tumours; RR, risk ratio; RT, radiotherapy; TAM, tamoxifen; VEM, vincristine, epirubicin, methotrexate

Clinical evidence tables for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

Table 16: Studies included in the review

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Alba, E., Calvo, L., Albanell, J., De la Haba, J. R., Arcusa Lanza, A., Chacon, J. I., Sanchez-Rovira, P., Plazaola, A., Lopez Garcia-Asenjo, J. A., Bermejo, B., Carrasco, E., Lluch, A., Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: Results from the GEICAM/2006-03, a multicenter, randomized, phase-II study, Annals of Oncology, 23, 3069-3074, 2012 **Ref Id** 610882 **Country/ies where the study was carried out** Spain **Study type** RCT **Aim of the study** To evaluate chemotherapy and hormone therapy as neoadjuvant treatment of people with	**Sample size** 95 **Characteristics** Gender: NR Age: median 51; range 32-74 Ethnicity: NR **Inclusion criteria** Aged >18 years with histologically confirmed ER+ (Allred 3-8), PR+, HER2-, cytokeratin 8/18+ breast cancer. Tumour size >2cm and/or axillary node involvement; ECOG performance status ≤1; normal cardiac, liver and renal function; adequate bone marrow **Exclusion criteria**	**Interventions** **Intervention arm:** neoadjuvant hormone therapy **Control arm:** neoadjuvant chemotherapy	**Details** **Intervention arm (NET):** oral exemestane 25 mg daily for 24 weeks. Pre-menopausal patients also received 3.6mg goserelin subcutaneously every 28 days for six cycles. After neoadjuvant treatment patients underwent surgery (mastectomy or BCS) including axillary node dissection (unless negative sentinel lymph node biopsy). **Control arm (NACT):** epirubicin 90 mg/m2 plus cyclophosphamide 600 mg/m^2 both administered intravenously (i.v.) on day 1 every 21 days, for four cycles followed by docetaxel 100 mg/m^2 administered i.v. on day 1 every 21 days for four cycles. Pre-menopausal patients also received 3.6mg goserelin subcutaneously every 28	**Results** **Whole sample:** **Breast conservation rates:** NET 27/48; NACT 22/47 **Changes in tumour size - clinical partial response:** NET 20/48; NACT 25/47 **Changes in tumour size - clinical complete response:** NET 3/48; NACT 6/47 **Pre-menopausal:** **Changes in tumour size - clinical response (partial or**	**Selection bias: allocation concealment** Not reported: Unclear **Selection bias: random sequence generation** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** Attrition rates and reasons similar between arms: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
luminal (ER+/PR+/HER2−/cytokeratin 8/18+) breast cancer **Study dates** Randomised March 2007 to December 2008 **Source of funding** Pfizer	Had already undergone treatment for current disease; previous anthracycline and/or taxane administration; receiving concurrent corticosteroids, ER modulators or HRT; inflammatory, bilateral or metastatic breast cancer; comorbid severe/uncontrolled systemic disease; of child-bearing potential and not using adequate contraception; history of cancer (other than skin or cervix) within last 10 years **Reported subgroups** pre-menopausal, post-menopausal, grade 1-2, grade 3		days for six cycles. After neoadjuvant treatment patients underwent surgery (mastectomy or BCS) including axillary node dissection (unless negative sentinel lymph node biopsy). Tumour response measured using MRI and evaluated according to RECIST criteria	**complete):** NET 12/27; NACT 18/24 **Post-menopausal:** **Changes in tumour size - clinical response (partial or complete):** NET 11/21; NACT 13/23 **Grade 1/2:** **Changes in tumour size - clinical response (partial or complete):** NET 19/38; NACT 28/41 **Grade 3:** **Changes in tumour size - clinical response (partial or complete):** NET 4/10; NACT 3/6	**Selective reporting** Low **Indirectness** None **Limitations** **Other information** GEICAM/2006-03 trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Mustacchi, G., Ceccherini, R., Milani, S., Pluchinotta, A., De Matteis, A., Maiorino, L., Farris, A., Scanni, A., Sasso, F., Bolognesi, A., Villa, E., Cobelli, S., Boni, C., Zadro, A., Cacioppo, C., Gambrosier, P., Schieppati, G., Sismondi, P., Genta, F., Traina, A., Malloci, A., Mansutti, M., Dellach, C., Fosser, V., Schittulli, F., Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: Long-term results of the phase III randomized controlled multicenter GRETA trial, Annals of Oncology, 14, 414-420, 2003 **Ref Id** 622492 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To evaluate the efficacy of tamoxifen as primary treatment compared with surgery followed by adjuvant tamoxifen	**Sample size** 474 recruited - 17 considered ineligible and 23 received opposite treatment **Characteristics** Gender: 100% women Age: median 76; range 65-90 Ethnicity: NR **Inclusion criteria** Aged ≥70 years; histological or cytological evidence of operable (T1, T2, T3a; N0 or N1; M0) invasive breast cancer **Exclusion criteria** Unfit for surgery/unavailable for follow-up; previous/concurrent malignancy (except treated skin cancer or in situ cervical cancer);	**Interventions** **Intervention arm:** primary tamoxifen **Control arm:** surgery followed by adjuvant tamoxifen	**Details** **Intervention arm (NET):** patients received 160 mg loading dose of tamoxifen on day 1, followed by 20 mg daily for 5 years **Control arm (No NET):** Surgery (82% radical) followed by tamoxifen 20 mg/day for 5 years Tumour response assessed using mammogram. Partial response defined as decrease >50% of two major diameters of the tumour compared with baseline	**Results** **Changes in tumour size - clinical complete response:** NET 21/235 **Changes in tumour size - clinical partial response:** NET 74/235 **OS (median 80 month follow-up):** O-E: 1.14; V: 68.32	**Selection bias: allocation concealment** Not reported: Unclear **Selection bias: random sequence generation** Permuted blocks: Low **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** Reason for ineligibility similar between arms. Slightly higher rate of individuals received opposite treatment in surgery arm. All

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
in women with operable breast cancer aged over 70 years **Study dates** Recruited March 1987 to June 1992 **Source of funding** Astra Zeneca and Progetto	prior chemotherapy and/or hormone therapy **Reported subgroups** None of interest				included in analysis (intention to treat): Low **Selective reporting** Low **Indirectness** Population: Unclear what proportion were ER+ - only assessed in 114 cases (of which 72% were ER+): serious **Limitations** **Other information** GRETA trial
Full citation Palmieri, C., Cleator, S., Kilburn, L. S., Kim, S. B., Ahn, S. H., Beresford, M., Gong, G., Mansi, J., Mallon, E., Reed, S., Mousa, K., Fallowfield, L., Cheang, M., Morden, J., Page, K., Guttery, D. S., Rghebi, B., Primrose, L., Shaw, J. A., Thompson, A. M., Bliss, J. M., Coombes, R. C., NEOCENT: a randomised feasibility and translational study comparing neoadjuvant endocrine therapy with chemotherapy in ER-rich postmenopausal primary breast cancer,	**Sample size** 44 randomised **Characteristics** Gender: 100% women Age: median 59.8 years Ethnicity: 61% South Korean, 32% Caucasian, 2% Asian British, 2% Black British	**Interventions** **Intervention arm:** neoadjuvant endocrine therapy **Control arm:** neoadjuvant chemotherapy	**Details** **Intervention arm (NET):** 2.5mg oral letrozole was given once daily for 18-23 weeks (until day before surgery) **Control arm (NACT):** FEC100C chemotherapy (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2 or FE75C: (5-fluorouracil 600 mg/m^2, epirubicin 75 mg/m^2,	**Results** **Changes in tumour size - radiological complete response:** NET 0/22; NACT 2/22 **Changes in tumour size - radiological partial response:** NET 13/22; NACT 10/22	**Selection bias: allocation concealment** Not reported: Unclear **Selection bias: random sequence generation** Not reported: Unclear **Selection bias: overall judgement** Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Breast Cancer Research and Treatment, 148, 581-590, 2014 **Ref Id** 616648 **Country/ies where the study was carried out** UK, South Korea **Study type** RCT **Aim of the study** To investigate the effectiveness and tolerability of endocrine therapy with an aromatase inhibitor compared with chemotherapy for downstaging ER+ breast cancer in post-menopausal women **Study dates** November 2008 to March 2011 **Source of funding** Cancer Research UK, Novartis, Grant Simpson Trust and the Lybian government	**Inclusion criteria** Post-menopausal women aged ≥70 years with ER+ invasive breast cancer. Tumour had to be ≥20mm and/or nodal disease ≥20mm **Exclusion criteria** Not able to biopsy primary tumour **Reported subgroups** All post-menopausal		cyclophosphamide 600 mg/m^2) given at 3 weekly intervals for 6 cycles. Patients were switched to docetaxel (100mg/m^2 every 3 weeks for 3 cycles) if disease was stable or progressive Radiological response ultrasound/mammogram. Evaluated according to RECIST criteria	**Changes in tumour size - clinical complete response:** NET 0/22; NACT 3/22 **Changes in tumour size - clinical partial response:** NET 20/22; NACT 14/22	**Performance bias** No blinding but unlikely to significantly impact results **Detection bias** High for HRQoL data, low for other outcomes due to objective nature **Attrition bias** Low **Selective reporting** Insufficient presentation of results for conservation rates and HRQoL **Indirectness** None **Limitations** Small sample size **Other information** NEOCENT trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Semiglazov,V.F., Semiglazov,V.V., Dashyan,G.A., Ziltsova,E.K., Ivanov,V.G., Bozhok,A.A., Melnikova,O.A., Paltuev,R.M., Kletzel,A., Berstein,L.M., Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer, Cancer, 110, 244-254, 2007 **Ref Id** 254914 **Country/ies where the study was carried out** Russia, Germany **Study type** RCT **Aim of the study** To evaluate the efficacy of neoadjuvant endocrine therapy with aromatase inhibitors compared with neoadjuvant chemotherapy in post-menopausal women with ER+ and/or PR+ breast cancer	**Sample size** 239 randomised **Characteristics** Gender: 100% women Age: NET median 68, NACT median 67, range NR Ethnicity: NR **Inclusion criteria** Post-menopausal women; untreated, histologically confirmed ER+ and/or PR+ invasive breast cancer; life expectancy ≥6 months; stage IIA to IIIB; adequate bone marrow, renal and hepatic function. **Exclusion criteria** Uncontrolled cardiac disease; bilateral or inflammatory breast cancer; other malignancies (except treated cervical cancer in situ or basal/squamous cell carcinoma of the skin;	**Interventions** **Intervention arm:** neoadjuvant endocrine therapy **Control arm:** neoadjuvant chemotherapy	**Details** **Intervention arm (NET):** patients were randomised within this arm to receive either 25mg exemestane or 1mg anastrozole daily for 3 months. Surgery was scheduled for 3 months from date patient first received medication **Control arm (NACT):** patients received chemotherapy with doxorubicin 60 mg/m^2 and paclitaxel 200 mg/m^2 every 3 weeks for 4 cycles. Surgery was scheduled for 3 months from date patient first received treatment with chemotherapy Complete response (regression 100%) and partial response (regression >50%) was determined by breast palpation, ultrasound, and mammography. Pathologically complete response also recorded at surgery. Palpable axillary involvement downgraded	**Results** **Breast conservation rates:** NET 40/121; NACT 28/118 **Changes in tumour size - clinical complete response:** NET 12/121; NACT 12/118 **Changes in tumour size - clinical partial response:** NET 66/121; NACT 63/118 **Changes in tumour size - ultrasound complete response:** NET 4/121; NACT 5/118 **Changes in tumour size - ultrasound partial response:** NET	**Selection bias: allocation concealment** Low **Selection bias: random sequence generation** Computer-generated permuted blocks: Low **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** Overall attrition low - rates and reasons similar across arms: Low **Selective reporting** Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Not reported **Source of funding** Federal Agency of Health and Social Development of the Russian Federation	concurrent hormone replacement therapy **Reported subgroups** All post-menopausal		clinically complete response to partial response.	45/121; NACT 50/118 **Changes in tumour size - mammography complete response:** NET 7/121; NACT 8/118 **Changes in tumour size - mammography partial response:** NET 66/121; NACT 66/118	**Indirectness** Population: 14% ER-: serious **Limitations** **Other information**
Full citation Marcus,D.M., Switchenko,J.M., Prabhu,R., O'Regan,R., Zelnak,A., Fasola,C., Mister,D., Torres,M.A., Neoadjuvant Hormonal Therapy is Associated with Comparable Outcomes to Neoadjuvant Chemotherapy in Post-Menopausal Women with Estrogen Receptor-Positive Breast Cancer, Frontiers in Oncology, 3, 317-, 2013 **Ref Id** 314704	**Sample size** 99 **Characteristics** Gender: 100% female Age: median 59; range NR Ethnicity: NR **Inclusion criteria** Post-menopausal (age >50 used as surrogate	**Interventions** **Intervention arm:** neoadjuvant endocrine therapy followed by surgery **Control arm:** neoadjuvant chemotherapy followed by surgery	**Details** **Intervention arm (NET):** The delivery, type, dose and duration of NET was determined by the treating medical oncologist. 93% received an aromatase inhibitor and 7% received tamoxifen; mean duration 8 months (0.5 to 60 months). **Control arm (NACT):** The delivery, type, dose and duration of NET was determined by the treating	**Results** **OS (4 year follow-up):** O-E: -0.98; V: 2.01	**Selection bias: allocation concealment** **Selection bias: random sequence generation** **Selection bias: overall judgement** **Performance bias** **Detection bias** **Attrition bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA **Study type** Retrospective cohort study **Aim of the study** To compare long-term outcomes of post-menopausal women with ER+ breast cancer treated with neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy. **Study dates** Treated 2004 to 2011 **Source of funding** Not reported	where menopausal status not reported) women with non-metastatic, non-inflammatory, ER+ breast cancer treated with neoadjuvant endocrine therapy (followed by surgery) or neoadjuvant chemotherapy (followed by surgery) at Emory University between 2004 and 2011. **Exclusion criteria** HER2+ **Reported subgroups** all post-menopausal		medical oncologist. 51% received both anthracycline and taxane, 38% received anthracycline only		**Selective reporting** **Indirectness** None **Limitations** **Selection:** Method of selection appropriate and likely to produce cohort representative of the specific population of interest. Outcomes not present at start of study. **Comparability:** Groups not comparable at baseline for T stage, N stage or grade (more advanced in NACT arm). Also higher rates of PR- and adjuvant radiotherapy in NACT arm. Not controlled for in analysis **Outcome:** Follow-up and outcome assessment adequate. Small sample size, particularly in NET arm. Wide variation in duration of endocrine therapy

BCS, breast conserving surgery; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FEC, fluorouracil, epirubicin, cyclophosphamide; HER2, human epidermal growth factor receptor 2; HRT, hormone replacement therapy; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NACT, neoadjuvant

chemotherapy; NET, neoadjuvant endocrine therapy; OS, overall survival; PR, progesterone receptor; RCT, randomised controlled trial; RECIST, response evaluation criteria in solid tumours

Clinical evidence tables for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

Table 17: Studies included in the review

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Abdel-Wahab, M., Wolfson, A., Raub, W., Mies, C., Brandon, A., Morrell, L., Lee, Y., Ling, S., Markoe, A., The importance of postoperative radiation therapy in multimodality management of locally advanced breast cancer: A phase II trial of neoadjuvant MVAC, surgery, and radiation, International Journal of Radiation Oncology Biology Physics, 40, 875-880, 1998 **Ref Id** 620840 **Country/ies where the study was carried out** USA **Study type** Cohort study **Aim of the study**	**Sample size** 55 **Characteristics** Gender: NR Age: Median 48, range 29-68 Ethnicity: 60% Caucasian, 40% African American **Inclusion criteria** People with clinically palpable T3, T4, N2, and N3 breast cancer who were over 18 years old **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	**Interventions** **Intervention arm:** postoperative radiotherapy to the chest wall ± regional lymph nodes **Control arm:** no postoperative radiotherapy	**Details** **Intervention arm (RT chest wall + nodes):** Neoadjuvant chemotherapy using IV MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) was given in a 28-day cycle. Day 1, methotrexate 30 mg/m2; day 2, doxorubicin 30 mg/m2 and vinblastine 3 mg/m2 IV push and cisplatin 70 mg/m2 IV infusion over 2 to 4 h; days 15 and 22, methotrexate 30 mg/m2 (IV push) and vinblastine 3 mg/m2 (IV). Calcium leucovorin (10 mg) was given orally 24 h after each dose of methotrexate. Dose modification, according to weekly blood counts and symptomatic toxicity, was allowed. Chemotherapy was given until either complete response (CR) was achieved or until the maximum response had been achieved (no change in tumour size for two consecutive treatment cycles). Participants then underwent modified radical mastectomy. Participants were then scheduled to undergo 6 courses of adjuvant MVAC chemotherapy. Participants who could not complete the 6	**Results** **LRR (median follow-up 47 months):** O-E: -2.50; V: 1.26 **OS (5 year follow-up):** O-E: 7.38; V: 6.31	**Selection** Method of selection appropriate and likely to produce representative cohort - all eligible people were offered participation. **Comparability** Unclear - characteristics of each arm were not reported **Outcome** Follow-up was adequate but unclear how outcome was assessed **Indirectness** Intervention: 67% received RT to the regional lymph nodes: serious **Limitations** Small number of individuals in no RT arm

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To determine the impact of postoperative radiation on locoregional relapse and overall survival rate in a multimodality protocol for locally advanced breast cancer **Study dates** Enrolled October 1990 to September 1993 **Source of funding** Not reported			courses of MVAC chemotherapy were switched to a less toxic CMF (cyclophosamide, methotrexate, 5FU) or CAF (cyclophosphamide, adriamycin, 5FU) chemotherapy. Postoperative radiation therapy to the chest wall was required 4 to 6 weeks after completing systemic therapy. Radiation to the axilla, supraclavicular region, and chest-wall boost were left to the discretion of the radiation oncologist. **Control arm (No RT):** Neoadjuvant chemotherapy using IV MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) was given in a 28-day cycle. Day 1, methotrexate 30 mg/m2; day 2, doxorubicin 30 mg/m2 and vinblastine 3 mg/m2 IV push and cisplatin 70 mg/m2 IV infusion over 2 to 4 h; days 15 and 22, methotrexate 30 mg/m2 (IV push) and vinblastine 3 mg/m2 (IV). Calcium leucovorin (10 mg) was given orally 24 h after each dose of methotrexate. Dose modification, according to weekly blood counts and symptomatic toxicity, was allowed. Chemotherapy was given until either complete response (CR) was achieved or until the maximum response had been achieved (no change in tumour size for two		**Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
			consecutive treatment cycles). Participants then underwent modified radical mastectomy. Participants were then scheduled to undergo 6 courses of adjuvant MVAC chemotherapy. Participants who could not complete the 6 courses of MVAC chemotherapy were switched to a less toxic CMF (cyclophosamide, methotrexate, 5FU) or CAF (cyclophosphamide, adriamycin, 5FU) chemotherapy.		
Full citation Garg, A. K., Oh, J. L., Oswald, M. J., Huang, E., Strom, E. A., Perkins, G. H., Woodward, W. A., Yu, T. K., Tereffe, W., Meric-Bernstam, F., Hahn, K., Buchholz, T. A., Effect of Postmastectomy Radiotherapy in Patients <35 Years Old With Stage II-III Breast Cancer Treated With Doxorubicin-Based Neoadjuvant Chemotherapy and Mastectomy, International Journal of Radiation Oncology Biology Physics, 69, 1478-1483, 2007 **Ref Id** 621303	**Sample size** 107 **Characteristics** Gender: NR Age: median NR, <35 years old Ethnicity: NR **Inclusion criteria** People <35 years old with stage II and II breast cancer on protocols for neoadjuvant doxorubicin-based chemotherapy and mastectomy	**Interventions** **Intervention arm:** postoperative radiotherapy to the chest wall and regional nodes **Control arm:** no postoperative radiotherapy	**Details** **Intervention arm (RT to chest wall + nodes):** All participants underwent computed tomography simulation and planning for optimal target coverage with minimal exposure to the lung and heart. The chest wall was usually treated with medial and lateral tangents using photons designed to include the entire chest wall (median dose 50 Gy). A separate supraclavicular anterior photon field was matched at the nondivergent superior border of the tangential fields designed to encompass the undissected Level III axilla and axillary apex (median dose 50 Gy). An electron field was often matched medially to the medial tangential field, with particular care to cover the internal mammary nodal region while	**Results** **Whole sample:** **LRR (5 year follow-up):** O-E: -7.56; V: 5.28 **OS (5 year follow-up):** O-E: 7.64; V: 12.56 **Clinical T2:** **LRR (5 year follow-up):** O-E: -2.06; V: 0.88 **OS (5 year follow-up):** O-E: -0.89; V: 0.96 **Clinical T3:**	**Selection** Insufficient information about method of selection so unclear if cohort is representative **Comparability** Groups not comparable and differences not controlled for. Participants in the PMRT group had a statistically greater percentage of Stage III tumours, greater percentage of lymphovascular space invasion, and Stage T4 disease.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA **Study type** Retrospective cohort study **Aim of the study** To assess the benefits of postmastectomy radiotherapy in patients <35 years old treated with doxorubicin-based neoadjuvant chemotherapy for Stage II–III breast cancer **Study dates** Treated 1975 to 2005 **Source of funding** Not reported	**Exclusion criteria** No additional criteria reported **Reported subgroups** Clinical T stage (2,3,4), Clinical N stage (0,1,2,3)		respecting critical structures, including the heart and lung (median dose 50 Gy). Finally, the chest wall was typically boosted (median dose 10 Gy) with electrons designed to include the mastectomy scar with an adequate margin. **Control arm (No RT):** No further details reported	**LRR (5 year follow-up):** O-E: -2.14; V: 1.20 **OS (5 year follow-up):** O-E: -3.82; V: 2.14 **Clinical T4:** **LRR (5 year follow-up):** O-E: -2.48; V: 1.04 **OS (5 year follow-up):** O-E: -3.41; V: 2.89 **Clinical N0:** **LRR (5 year follow-up):** O-E: -1.36; V: 0.46 **OS (5 year follow-up):** O-E: -2.95; V: 1.38 **Clinical N1:** **LRR (5 year follow-up):** O-E: -1.97; V: 2.06	**Outcome** Assessment of outcomes and follow-up were adequate **Indirectness** None **Limitations** Small number of participants in no RT arm **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				OS (5 year follow-up): O-E: 0.84; V: 4.37 **Clinical N2:** **LRR (5 year follow-up):** O-E: -1.73; V: 0.62 **OS (5 year follow-up):** O-E: -1.45; V: 0.85 **Clinical N3:** **LRR (5 year follow-up):** O-E: -0.54; V: 0.25 **OS (5 year follow-up):** O-E: -0.46; V: 0.61	
Full citation Huang, E. H., Tucker, S. L., Strom, E. A., McNeese, M. D., Kuerer, H. M., Buzdar, A. U., Valero, V., Perkins, G. H., Schechter, N. R., Hunt, K. K., Sahin, A. A., Hortobagyi, G. N., Buchholz, T. A., Postmastectomy radiation improves local-regional	**Sample size** 676 **Characteristics** Gender: NR Age: Median 49, range NR Ethnicity: NR	**Interventions** **Intervention arm:** postoperative radiotherapy to the chest wall ± draining lymphatics **Control arm:** no	**Details** **Intervention arm (RT to chest wall + nodes):** All participants received doxorubicin as part of a combination neoadjuvant chemotherapy regimen; 15% also received a taxane. FAC chemotherapy consisted of 500 mg/m2 fluorouracil given on days 1 and 4 or 8, 50 mg/m2 doxorubicin given	**Results** **Whole sample:** **LRR (10 year follow-up):** O-E: -14.64; V: 14.16 **OS (10 year follow-up):** O-E: 13.98; V: 56.53	**Selection** Insufficient information about method of selection in original studies so unclear if cohort is representative **Comparability**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy.[Erratum appears in J Clin Oncol. 2005 Jan 1;23(1):248], Journal of clinical oncology, 22, 4691-9, 2004 **Ref Id** 621447 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To evaluate the efficacy of radiation in people treated with neoadjuvant chemotherapy and mastectomy **Study dates** 1974 to 2000	**Inclusion criteria** Inclusion criteria not reported - data comes from six prospective trials that investigated the role of doxorubicin-based neoadjuvant chemotherapy for people with non-metastatic, non-inflammatory breast cancer **Exclusion criteria** None reported **Reported subgroups** Clinical T stage (1,2,3,4); Clinical N stage (0,1,2/3)	postoperative radiotherapy	as a day 1 bolus or as a 48- to 72-hour continuous infusion, and 500 mg/m2 cyclophosphamide given on day 1. For those participants receiving dose-escalated FAC, the doses of these drugs were increased to 600, 60, and 1,000 mg/m2, respectively. The VACP regimen consisted of 1.5 mg/m2 vincristine, 60 to 75 mg/m2 doxorubicin, 600 to 750 mg/m2 cyclophosphamide, and 40mg prednisone. Lastly, the AT regimen consisted of 60 mg/m2 doxorubicin and 60 mg/m2 docetaxel given as IV boluses. All participants were treated with mastectomy; median number of recovered lymph nodes were 15. After neoadjuvant chemotherapy and mastectomy 95% received adjuvant chemotherapy; 34% also received tamoxifen. Postoperative radiotherapy included the chest wall and typically draining lymphatics (median dose 50Gy) followed by a chest wall boost (median dose 10Gy). **Control arm:** All participants received doxorubicin as part of a combination neoadjuvant chemotherapy regimen; 15% also received a taxane. FAC chemotherapy consisted of 500 mg/m2 fluorouracil given on days 1 and 4	**Clinical T1**: **LRR (10 year follow-up):** O-E: 0.28; V: 0.21 **Clinical T2:** **LRR (10 year follow-up):** O-E: -1.33; V: 2.57 **Clinical T3:** **LRR (10 year follow-up):** O-E: -5.81; V: 3.53 **Clinical T4:** **LRR (10 year follow-up):** O-E: -9.20; V: 5.59 **Clinical N0:** **LRR (10 year follow-up):** O-E: -5.02; V: 4.17 **Clinical N1:** **LRR (10 year follow-up):** O-E: -4.20; V: 5.06 **Clinical N2/3:**	RT arm: more advanced clinical T, N and total stage; poorer response to neoadjuvant chemo; more positive nodes and positive margins **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Because of the limited number of participants in some subgroup analyses, cannot conclude a lack of benefit from radiation, particularly for people with earlier stage disease or lesser pathological extent of disease **Other information** People from The University of Texas M.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding National Cancer Institute grants CA16672 and T32CA77050			or 8, 50 mg/m2 doxorubicin given as a day 1 bolus or as a 48- to 72-hour continuous infusion, and 500 mg/m2 cyclophosphamide given on day 1. For those participants receiving dose-escalated FAC, the doses of these drugs were increased to 600, 60, and 1,000 mg/m2, respectively. The VACP regimen consisted of 1.5 mg/m2 vincristine, 60 to 75 mg/m2 doxorubicin, 600 to 750 mg/m2 cyclophosphamide, and 40mg prednisone. Lastly, the AT regimen consisted of 60 mg/m2 doxorubicin and 60 mg/m2 docetaxel given as IV boluses. All participants were treated with mastectomy; median number of recovered lymph nodes were 15. After neoadjuvant chemotherapy and mastectomy 95% received adjuvant chemotherapy; 34% also received tamoxifen.	**LRR (10 year follow-up):** O-E: -7.39; V: 3.61	D. Anderson Cancer Center
Full citation Le Scodan, R., Selz, J., Stevens, D., Bollet, M. A., De La Lande, B., Daveau, C., Lerebours, F., Labib, A., Bruant, S., Radiotherapy for stage II and stage III breast cancer patients with negative lymph nodes after	**Sample size** 134 **Characteristics** Gender: NR Age: mean 49.9; range 28-71 Ethnicity: NR	**Interventions** **Intervention arm:** post mastectomy radiotherapy to chest wall and regional lymph nodes	**Details** **Intervention arm (RT to chest wall + nodes):** All NAC was anthracycline based; mastectomy included axillary dissection. Post mastectomy radiotherapy targeted the chest wall, supraclavicular lymph nodes, and internal mammary nodes to a total dose of 45–50Gy (daily fractions of	**Results** **LRR (10 year follow-up):** O-E: -1.82; V: 1.98 **DFS (10 year follow-up):** O-E: 2.89; V: 6.50	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Significantly more advanced T stage and

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
preoperative chemotherapy and mastectomy, International Journal of Radiation Oncology Biology Physics, 82, e1-e7, 2012 **Ref Id** 621640 **Country/ies where the study was carried out** France **Study type** Retrospective cohort study **Aim of the study** To evaluate the effect of postmastectomy radiotherapy (PMRT) in people with stage II-III breast cancer with negative lymph nodes (pN0) after neoadjuvant chemotherapy (NAC). **Study dates** Received neoadjuvant chemotherapy between January 1990 and December 2004	**Inclusion criteria** People with stage II or stage III breast cancer that received neoadjuvant chemotherapy at the Rene Huguenin Cancer Center (Saint Cloud, France). Had to have undergone mastectomy and have pathologic N0 status (pN0) after neoadjuvant chemotherapy **Exclusion criteria** No additional criteria reported **Reported subgroups** All participants pN0	**Control arm:** no post mastectomy radiotherapy	1.8-2.0Gy). PMRT typically used a photon field to treat the supraclavicular fossa/axillary apex, a mixed photon and electron field to treat the internal mammary chains, and an electron field to treat the chest wall. **Control arm (No RT):** All NAC was anthracycline based; mastectomy included axillary dissection.	**OS (10 year follow-up):** O-E: 2.91; V: 4.20	total clinical stage in radiotherapy arm. Not controlled for in main analysis **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Fairly small sample size. Lack of benefit associated with PMRT could have resulted, in part, from the limited number of participants and the significant differences in the known prognostic factors (e.g., clinical T or N stage at diagnosis) between the PMRT and no-PMRT groups, favouring the no-PMRT cohort. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Not reported					
Full citation Liu, J., Mao, K., Jiang, S., Jiang, W., Chen, K., Kim, B. Y., Liu, Q., Jacobs, L. K., The role of postmastectomy radiotherapy in clinically node-positive, stage II-III breast cancer patients with pathological negative nodes after neoadjuvant chemotherapy: an analysis from the NCDB, Oncotarget, 7, 24848-59, 2016 **Ref Id** 621680 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To identify the effectiveness of PMRT in terms of overall survival for clinically node-	**Sample size** 1560 **Characteristics** Gender: 100% women Age: median 50, range 20-88 Ethnicity: 76% Caucasian, 18% Black **Inclusion criteria** Women 18 years or older, clinically node-positive and stage II-III breast cancer, treated with NAC and mastectomy with pathologically confirmed complete nodal response (ypN0) **Exclusion criteria** People with positive or unknown surgical margin, pathological tumour size > 5 cm after NAC, distant metastatic disease, prior malignancy, unknown clinical	**Interventions** **Intervention arm:** post mastectomy radiotherapy to chest wall and draining lymphatics **Control arm:** No post mastectomy radiotherapy	**Details** **Intervention arm (RT to chest wall + nodes):** radiation targets included chest wall and draining lymphatics, with or without a chest wall boost. The median dose of radiation was 50.4Gy. **Control arm (No RT):** No details reported	**Results** **Whole sample (All pN0):** **OS (5 year follow-up):** O-E: 11.38; V: 53.60 **Clinical T stage T1/T2:** **OS (5 year follow-up):** O-E: -4.55; V: 21.74 **Clinical T stage T3/T4:** **OS (5 year follow-up):** O-E: -13.93; V: 38.62 **Clinical N stage N1:** **OS (5 year follow-up):** O-E: -9.10; V: 48.47 **Clinical N stage N2/N3:**	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** RT arm diagnosed later, more advanced clinical stage (total, N and T). More ER+ and PR-, multi-agent chemotherapy. Less hormone therapy. Not controlled for in main analysis **Outcome** Follow-up adequate; outcome assessment unclear. **Indirectness** None **Limitations**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
positive, stage II-III breast cancer patients with ypN0 after neoadjuvant chemotherapy **Study dates** Diagnosed 1998 to 2012 **Source of funding** Natural Science Foundation of Guangdong Province (2014A030310507); and the Key Laboratory of Malignant Tumor Molecular Mechanism and Translational Medicine of Guangzhou Bureau of Science and Information Technology ([2013]163); and the Key Laboratory of Malignant Tumor Gene Regulation and Target Therapy of Guangdong Higher Education Institutes (KLB09001).	or pathological tumour/node stage, preoperative or intraoperative radiotherapy, or radiotherapy not for chest wall and draining lymphatics **Reported subgroups** All participants pN0; Clinical T stage (T1/T2,T3/T4), Clinical N stage (N1,N2/N3), Pathological T stage (T0/Tis,T1/T2)			**OS (5 year follow-up):** O-E: -3.45; V: 14.13 **Pathological T stage T0/Tis:** **OS (5 year follow-up):** O-E: 0.65; V: 22.29 **Pathological T stage T1/T2:** **OS (5 year follow-up):** O-E: -13.04; V: 40.75	The NCDB has no recurrence data, so cannot affirm a lack of benefit from PMRT for some subgroups of women simply based on OS alone. This is especially the case for participants with earlier clinical stage disease, where disease control and free from recurrence would more likely be the primary endpoint of interest **Other information**
Full citation McGuire, S. E., Gonzalez-Angulo, A. M., Huang, E. H., Tucker, S. L., Kau, S. W. C.,	**Sample size** 106	**Interventions** **Intervention arm:** post mastectomy radiotherapy to	**Details** **Intervention arm (RT to chest wall + nodes):** 92% received an anthracycline as a component of the neoadjuvant chemotherapy,	**Results** **LRR (10 year follow-up):** O-E: -1.04; V: 1.53	**Selection** Method of selection appropriate and likely

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Yu, T. K., Strom, E. A., Oh, J. L., Woodward, W. A., Tereffe, W., Hunt, K. K., Kuerer, H. M., Sahin, A. A., Hortobagyi, G. N., Buchholz, T. A., Postmastectomy Radiation Improves the Outcome of Patients With Locally Advanced Breast Cancer Who Achieve a Pathologic Complete Response to Neoadjuvant Chemotherapy, International Journal of Radiation Oncology Biology Physics, 68, 1004-1009, 2007 **Ref Id** 621766 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To investigate the role of post mastectomy radiation therapy in women with breast cancer who achieved a pathologic complete response (pCR) to neoadjuvant chemotherapy	**Characteristics** Gender: 100% women Age: median 46; range 23-74 Ethnicity: NR **Inclusion criteria** Women who had achieved a pCR after receiving neoadjuvant chemotherapy who had mastectomy **Exclusion criteria** Inflammatory breast cancer **Reported subgroups** All participants had pCR (conservative definition - pT0/Tis)	chest wall and draining lymphatics **Control arm:** no post mastectomy radiotherapy	and 38% received a taxane either pre- or postoperatively. All participants underwent a modified radical mastectomy that included a level I or II axillary dissection. Post mastectomy radiotherapy typically targeted the chest wall and draining lymphatics with 50 Gy in 25 fractions over 5 weeks, followed by a boost to the chest wall consisting of 10 Gy in five fractions over 1 week. The undissected draining lymphatics were typically treated with two separate fields, a photon field targeting the supraclavicular fossa/axillary apex, and an electron field targeting the internal mammary chain and medial chest wall. **Control arm (No RT):** 92% received an anthracycline as a component of the neoadjuvant chemotherapy, and 38% received a taxane either pre- or postoperatively. All participants underwent a modified radical mastectomy that included a level I or II axillary dissection.	**OS (10 year follow-up) - stage III participants only:** O-E: -5.47; V: 3.00	to produce representative cohort **Comparability** RT arm more advanced cancer but analysis showed that clinical T and N stage did not affect LRR **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Small sample size, particularly in control arm **Other information** People from The University of Texas M. D. Anderson Cancer Center

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Received neoadjuvant chemotherapy between 1982 and 2002 **Source of funding** National Cancer Institute Grants Nos. CA16672 and T32CA77050, the Nellie B. Connally Breast Cancer Research Fund, and the Arlette and William Coleman Foundation					
Full citation Meattini, I., Cecchini, S., Di Cataldo, V., Saieva, C., Francolini, G., Scotti, V., Bonomo, P., Mangoni, M., Greto, D., Nori, J., Orzalesi, L., Casella, D., Simoncini, R., Fambrini, M., Bianchi, S., Livi, L., Postmastectomy radiotherapy for locally advanced breast cancer receiving neoadjuvant chemotherapy, BioMed Research International, 2014, 719175, 2014	**Sample size** 170 **Characteristics** Gender: NR Age: median 48.9; range 24-76 Ethnicity: NR **Inclusion criteria** Adults with breast cancer who received neoadjuvant	**Interventions** **Intervention arm:** post mastectomy radiotherapy to chest wall and draining lymphatics **Control arm:** no post mastectomy radiotherapy	**Details** **Intervention arm (RT to chest wall + nodes):** 99% received anthracyclines as part of combination neoadjuvant chemotherapy regimen; 41% also received a taxane. Most commonly administered chemotherapy regimens were FEC and ET; FEC chemotherapy consisted of 500 mg/m2 5-fluorouracil, 75mg/m2 epirubicin, and 500mg/m2 cyclophosphamide, given on day 1.The ET regimen consisted of 75 mg/m2 epirubicin and 75mg/m2 docetaxel, given on day 1. The	**Results** **Whole sample:** **LRR (median follow-up 7.7 years):** O-E: -1.44; V: 6.46 **OS (median follow-up 7.7 years):** O-E: -0.90; V: 17.65 **Clinical T stage T2:**	**Selection** Method of selection and likely to produce representative cohort **Comparability** Larger number of irradiated participants had greater clinical and pathological T, N, and combined TNM stage. **Outcome**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Ref Id 621771 **Country/ies where the study was carried out** Italy **Study type** Cohort study **Aim of the study** To identify major prognostic factors in locally advanced breast cancer with emphasis on postmastectomy radiotherapy **Study dates** Treated with neoadjuvant chemotherapy between 1997 and 2011 **Source of funding** Not reported	chemotherapy and mastectomy **Exclusion criteria** Previous solid tumours, age less than 18, and BC recurrences or contralateral tumour **Reported subgroups** Clinical T stage (T2,T3,T4), Clinical N stage (N0,N1,N2), Pathological T stage (Tx/Tis,T2,T3,T4), Pathological N stage (N0,N1,N2,N3)		median number of chemotherapy cycles received was 4 (mean, 4.7; range, 2–6). All participants received mastectomy. Post mastectomy radiotherapy treatment volumes typically included the chest wall and draining lymphatics, consisting in the supraclavicular (SCV) and infraclavicular (ICV) nodal region (total dose 50Gy; 2Gy daily fractions), with mixed photon and electron beams technique, chosen at physician discretion. Did not irradiate mammary internal nodal region, unless pathologically involved. **Control arm (no RT):** 99% received anthracyclines as part of combination neoadjuvant chemotherapy regimen; 41% also received a taxane. Most commonly administered chemotherapy regimens were FEC and ET; FEC chemotherapy consisted of 500 mg/m2 5-fluorouracil, 75mg/m2 epirubicin, and 500mg/m2 cyclophosphamide, given on day 1.The ET regimen consisted of 75 mg/m2 epirubicin and 75mg/m2 docetaxel, given on day 1. The median number of chemotherapy cycles received was 4 (mean, 4.7; range, 2–6). All participants received mastectomy.	**LRR (median follow-up 7.7 years):** O-E: -1.35; V: 0.75 **Clinical T stage T3:** **LRR (median follow-up 7.7 years):** O-E: -3.62; V: 2.21 **Clinical T stage T4:** **LRR (median follow-up 7.7 years):** O-E: 2.26; V: 2.46 **Clinical N stage N0:** **LRR (median follow-up 7.7 years):** O-E: -0.52; V: 1.25 **Clinical N stage N1:** **LRR (median follow-up 7.7 years):** O-E: -2.25; V: 2.44	Follow-up adequate, outcome assessment unclear **Indirectness** Intervention: 86% received RT to chest wall + nodes, 14% received RT to chest wall only: serious **Limitations** Relatively small sample size. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Clinical N stage N2: **LRR (median follow-up 7.7 years):** O-E: -0.21; V: 1.67 **Pathological T stage Tx/Tis:** **LRR (median follow-up 7.7 years):** O-E: -0.92; V: 0.75 **Pathological T stage T2:** **LRR (median follow-up 7.7 years):** O-E: -2.47; V: 2.25 **Pathological T stage T3:** **LRR (median follow-up 7.7 years):** O-E: -1.46; V: 1.19 **Pathological T stage T4:** **LRR (median follow-up 7.7**	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				years): O-E: 0.80; V: 1.36 **Pathological N stage N0:** **LRR (median follow-up 7.7 years):** O-E: -0.61; V: 0.42 **Pathological N stage N1:** **LRR (median follow-up 7.7 years):** O-E: 0.74; V: 2.24 **Pathological N stage N2:** **LRR (median follow-up 7.7 years):** O-E: -2.25; V: 2.56 **Pathological N stage N3:** **LRR (median follow-up 7.7 years):** O-E: -0.51; V: 0.70	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Nagar, H., Boothe, D., Ginter, P. S., Sison, C., Vahdat, L., Shin, S., Smith, M., Chao, K. S. C., Nori, D., Hayes, M. K., Disease-free survival according to the use of postmastectomy radiation therapy after neoadjuvant chemotherapy, Clinical breast cancer, 15, 128-134, 2015 **Ref Id** 582685 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To determine predictors of recurrence for people treated with neoadjuvant chemotherapy and mastectomy according to the use of post mastectomy radiation therapy	**Sample size** 161 **Characteristics** Gender: NR Age: mean 51; range NR Ethnicity: 62% Caucasian, 9% African-American, 1% Asian, 6% Hispanic **Inclusion criteria** Clinically staged T1 to T3/N0 to N3 M0 breast cancer patients treated with neoadjuvant chemotherapy and mastectomy **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	**Interventions** **Intervention arm:** radiotherapy to the chest wall and regional nodes **Control arm:** no radiotherapy	**Details** **Intervention arm (RT to chest wall + nodes):** All participants received preoperative chemotherapy. Most (93%) participants received anthracycline-based chemotherapy, with approximately 80% of participants receiving a combination of anthracycline and taxane-based chemotherapy. All participants with HER2-positive disease received adjuvant trastuzumab, but approximately half (49%) of participants with HER2-positive disease received trastuzumab preoperatively at the discretion of the medical oncologist. All participants underwent mastectomy. Axillary lymph node dissection was performed in 143 (89%) participants and sentinel lymph node biopsy alone was performed in 18 (11%) participants at the time of surgery. The median number of lymph nodes removed during surgery was 12 (range, 0-40). Post mastectomy radiotherapy radiation was delivered to the chest wall and regional lymph nodes (axilla, supraclavicular fossa, and internal mammary lymph nodes).	**Results** **DFS (5 year follow-up):** O-E: -3.41; V: 4.97	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** More advanced clinical N stage in RT arm. Not controlled for in analysis **Outcome** Follow-up adequate, outcome assessment unclear **Indirectness** None **Limitations** Relatively small sample size, particularly for control arm and relatively short follow-up period **Other information** University of Texas M.D. Anderson Cancer Center

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Treated 2003 to 2010 **Source of funding** Not reported			**Control arm (No RT):** All participants received preoperative chemotherapy. Most (93%) participants received anthracycline-based chemotherapy, with approximately 80% of participants receiving a combination of anthracycline and taxane-based chemotherapy. All participants with HER2-positive disease received adjuvant trastuzumab, but approximately half (49%) of participants with HER2-positive disease received trastuzumab preoperatively at the discretion of the medical oncologist. All participants underwent mastectomy. Axillary lymph node dissection was performed in 143 (89%) participants and sentinel lymph node biopsy alone was performed in 18 (11%) participants at the time of surgery. The median number of lymph nodes removed during surgery was 12 (range, 0-40).		
Full citation Nagar, H., Mittendorf, E. A., Strom, E. A., Perkins, G. H., Oh, J. L., Tereffe, W.,	**Sample size** 162	**Interventions** **Intervention arm:** radiotherapy to the chest wall	**Details** **Intervention arm (RT to chest wall + nodes):** All participants received preoperative chemotherapy. The majority (92%)	**Results** **Whole sample (Clinical T**	**Selection** Method of selection appropriate and likely

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Woodward, W. A., Gonzalez-Angulo, A. M., Hunt, K. K., Buchholz, T. A., Yu, T. K., Local-regional recurrence with and without radiation therapy after neoadjuvant chemotherapy and mastectomy for clinically staged T3N0 breast cancer, International Journal of Radiation Oncology Biology Physics, 81, 782-787, 2011 **Ref Id** 621835 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To determine local-regional recurrence (LRR) risk according to whether post mastectomy radiation therapy (PMRT) was used to treat breast cancer patients with clinical T3N0 disease who received neoadjuvant chemotherapy (NAC) and mastectomy	**Characteristics** Gender: NR Age: RT median 53; no RT median 47; range NR Ethnicity: NR **Inclusion criteria** Breast cancer patients treated with neoadjuvant chemotherapy and mastectomy with clinically staged T3N0 tumours **Exclusion criteria** No additional criteria reported **Reported subgroups** All clinical T3N0; pathological N stage (N0)	and regional nodes **Control arm:** no radiotherapy	of participants received anthracycline-based chemotherapy, with approximately one-third (37%) of participants receiving a combination of anthracycline and taxane. A small group (8%) of participants received only taxane-based chemotherapy. All participants underwent mastectomy. Post mastectomy radiation was delivered to the chest wall and regional nodal basins (high axilla and supraclavicular fossa, with or without the internal mammary chain). Typically, the lateral chest wall was treated with medial-lateral tangential photon fields, while the medial chest wall and underlying internal mammary chain were treated with an anteroposterior oblique electron field. The axillary apex and supraclavicular fossa were treated with an anteroposterior oblique photon field. 43% of participants received either tamoxifen or an aromatase inhibitor. **Control arm (No RT):** All participants received preoperative chemotherapy. The majority (92%) of participants received anthracycline-based chemotherapy, with approximately one-third (37%) of participants receiving a combination of anthracycline and taxane. A small	**stage 3, Clinical N stage 0):** **LRR (5 year follow-up):** O-E: -5.64; V: 2.94 **Pathological N stage N0:** **LRR (5 year follow-up):** O-E: -2.14; V: 1.29	to produce representative cohort **Comparability** Radiation arm significantly older and had significantly more positive nodes after neoadjuvant chemotherapy. Not controlled for in analysis **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Relatively small sample size, particularly for control arm **Other information** University of Texas M.D. Anderson Cancer Center

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Treated 1985 to 2004 **Source of funding** Not reported			group (8%) of participants received only taxane-based chemotherapy. All participants underwent mastectomy. 43% of participants received either tamoxifen or an aromatase inhibitor.		
Full citation Rusthoven, C. G., Rabinovitch, R. A., Jones, B. L., Koshy, M., Amini, A., Yeh, N., Jackson, M. W., Fisher, C. M., The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysis, Annals of oncology, 27, 818-27, 2016 **Ref Id** 566819 **Country/ies where the study was carried out** USA **Study type**	**Sample size** 10,283 (only interested in those that had mastectomy) **Characteristics** Gender: 100% women Age: NR Ethnicity: 78% Caucasian, 17% Black **Inclusion criteria** Women ≥18 years with cT1–3, cN1, M0 breast cancer treated with multi-agent neoadjuvant chemotherapy followed by mastectomy or breast-conserving surgery (only interested in mastectomy cohort)	**Interventions** **Intervention arm:** post mastectomy radiotherapy to chest wall ± regional nodes **Control arm:** no radiotherapy	**Details** **Intervention arm (RT to chest wall + nodes):** All participants received neoadjuvant chemotherapy and mastectomy. No information available about types of chemotherapy received or hormonal therapy. Post mastectomy radiotherapy targeted the chest wall ± regional nodes. **Control arm:** All participants received neoadjuvant chemotherapy and mastectomy. No further details reported.	**Results** **Pathological N stage N0; Clinical T stage T1-T2:** **OS (median 39 month follow-up):** O-E: -14.19; V: 29.69 **Pathological N stage N0; Clinical T stage T3:** **OS (median 39 month follow-up):** O-E: -6.88; V: 27.98 **Pathological N stage N1:**	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** RT arm younger, diagnosed later, more advanced clinical T stage and pathological N stage, higher rates ER positive. Not controlled for in analysis **Outcome** Outcome assessment adequate. Follow-up limited **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Retrospective cohort study **Aim of the study** To evaluate the impact of post mastectomy radiotherapy for women with clinically node-positive breast cancer treated with neoadjuvant chemotherapy **Study dates** Diagnosed 2003 to 2011 **Source of funding** Not reported	**Exclusion criteria** No additional criteria reported **Reported subgroups** pN0cT1-T2, pN0cT3, pN1, pN2-N3, pN+cT1-T2, pN+cT3			**OS (median 39 month follow-up):** O-E: -27.74; V: 153.85 **Pathological N stage N2-N3:** **OS (median 39 month follow-up):** O-E: -54.18; V: 139.42 **Pathological N+; Clinical T stage T1-T2:** **OS (median 39 month follow-up):** O-E: -26.85; V: 152.98 **Pathological N+; Clinical T stage T3:** **OS (median 39 month follow-up):** O-E: -50.90; V: 137.72	Intervention: unclear what proportion received radiotherapy to regional nodes: serious **Limitations** Details regarding RNI fields and techniques, locoregional control, and disease-free survival were unavailable. Data regarding the specific chemotherapy and hormone therapies administered were unavailable **Other information** National Cancer Database (NCDB)
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Selection**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Shim, S. J., Park, W., Huh, S. J., Choi, D. H., Shin, K. H., Lee, N. K., Suh, C. O., Keum, K. C., Kim, Y. B., Ahn, S. D., Kim, S. S., Ha, S. W., Chie, E. K., Kim, K., Shin, H. S., Kim, J. H., Lee, H. S., The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: A multicenter, retrospective study (KROG 12-05), International Journal of Radiation Oncology Biology Physics, 88, 65-72, 2014 **Ref Id** 552922 **Country/ies where the study was carried out** Korea **Study type** Retrospective cohort study **Aim of the study** To investigate the role of post mastectomy radiation therapy after neoadjuvant	151 **Characteristics** Gender: NR Age: median 47; range 27-78 Ethnicity: NR **Inclusion criteria** Breast cancer patients with tumour size >5 cm or axillary LN metastasis who achieved pN0 after neoadjuvant chemotherapy and had mastectomy **Exclusion criteria** People with distant metastases, clinically positive supraclavicular or internal mammary lymph nodes, inflammatory or bilateral breast cancer, another previous or concurrent malignancy except for thyroid cancer, previous chemotherapy, or previous radiation therapy were excluded	**Intervention arm:** post mastectomy radiotherapy to chest wall and regional nodes **Control arm:** no radiotherapy	**Intervention arm (RT to chest wall + nodes):** All participants received preoperative chemotherapy. The most common NAC regimen was a combination of anthracycline and taxane, followed by anthracycline-based and taxane-based chemotherapy. All participants underwent mastectomy and the majority received complete axillary lymph node dissection. Adjuvant chemotherapy was performed in 72% of participants. Post mastectomy radiotherapy was delivered to the chest wall and regional nodal basins (axilla and supraclavicular fossa, with or without the internal mammary chain). Only 7 participants (4.6%) did not receive supraclavicular fossa irradiation; 57 participants (37.8%) received internal mammary irradiation. A total radiation therapy dose of 45-50 Gy was delivered to the chest wall, supraclavicular lymph nodes, and internal mammary nodes. The standard schedule consisted of daily fractions of 1.8-2.0 Gy. The chest wall was treated with a photon tangential field or reverse hockey stick (photon-electron field). The supraclavicular fossa was treated with an anteroposterior oblique photon field.	**LRR (median follow-up 57 months):** O-E: -1.57; V: 1.17 **DFS (median follow-up 57 months):** O-E: -1.46; V: 3.61 **OS (median follow-up 57 months):** O-E: -1.21; V: 2.47	Method of selection appropriate and likely to produce representative cohort **Comparability** Greater percentage of participants in the non-PMRT group had lymphovascular space invasion. Not controlled for in analysis **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Relatively small sample size, particularly in control arm. The data were collected retrospectively from multiple institutions, introducing heterogeneity in chemotherapy

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
chemotherapy in clinical stage II-III breast cancer patients with pN0 **Study dates** Received neoadjuvant chemotherapy between January 1998 and December 2009 **Source of funding** Not reported	**Reported subgroups** All pN0		**Control arm (No RT):** All participants received preoperative chemotherapy. The most common NAC regimen was a combination of anthracycline and taxane, followed by anthracycline-based and taxane-based chemotherapy. All participants underwent mastectomy and the majority received complete axillary lymph node dissection. Adjuvant chemotherapy was performed in 72% of participants.		regimens and RT techniques **Other information** KROG 12-05

AT, doxorubicin, docetaxel; BC, breast cancer; CAF, cyclophosphamide, adriamycin, 5FU; CR, complete response; CMF, cyclophosamide, methotrexate, 5FU; DFS, disease-free survival; ER, oestrogen receptor; ET, epirubicin, docetaxel; FAC, fluorouracil, doxorubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; Gy; Gray; HER2, Human epidermal growth factor receptor 2; IV, intravenous; IVC, infraclavicular; LN, lymph node; LRR, locoregional recurrence; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; NAC, neoadjuvant chemotherapy; OS, overall survival; PMRT, postmastectomy radiotherapy; PR, progesterone receptor; RT, radiotherapy; SVC, supraclavicular; VACP, vincristine, doxorubicin, cyclophosphamide, prednisone

Clinical evidence tables for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

Table 18: Studies included in the review

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Zhang, P., Yin, Y., Mo, H., Zhang, B., Wang, X., Li, Q., Yuan, P., Wang, J., Zheng, S., Cai, R., Ma, F., Fan, Y., Xu, B., Better pathologic complete response and relapse-free survival after carboplatin plus paclitaxel compared with epirubicin plus paclitaxel as neoadjuvant chemotherapy for locally advanced triple-negative breast cancer: A randomized phase 2 trial, Oncotarget, 7, 60647-60656, 2016 **Ref Id** 568179 **Country/ies where the study was carried out** China **Study type** Randomized Controlled Trial **Aim of the study**	**Sample size** 91 **Characteristics** Mean Age: 47 years, Female/Male =91/0 Intervention (PC) (n=47); Controls (EP) (n=44) Tumour Stage: Stage II=31, Stage III=60 **Inclusion criteria** 1) women aged 18-75 years; 2) ECOG score 0-1 3) pathologically confirmed breast invasive ductal cancer by core needle biopsy, ER/PR/Her-2 negative by immunohistochemistry (IHC) 4) clinical stage IIA-IIIC with NAC indication 5) measurable lesions	**Interventions** PC regimen: Paclitaxel 175 mg/m^2 on day 1 plus carboplatin Area Under the Curve (AUC) = 5 on day 2, both administered via intravenous infusion (IV),every 3 weeks for 4-6 cycles. EP regimen :Epirubicin 75 mg/m^2 on day 1 and paclitaxel 175 mg/m^2 on day 2, both IV, every 3 weeks for 4-6 cycles.	**Details** Intervention arm: paclitaxel (175 mg/m^2, day1) plus carboplatin (Area Under the Curve = 5, day 2) (PC) Control arm: epirubicin (75mg/m^2, day1) plus paclitaxel (175 mg/m^2, day2) (EP) as NAC every three weeks for 4-6 cycles. Patients underwent modified radical mastectomy or breast-conserving surgery within four weeks from the last NAC cycle.	**Results** Objective response rate PC (intervention) arm: 89.4% , Control (EP) arm: 79.5%, P = 0.195. pCR rate in the PC arm was significantly higher (38.6% vs. 14.0%, P = 0.014). The median follow-up time was 55.0 months. 5-year RFS were 77.6% and 56.2%, significantly higher in the PC arm, P = 0.043. No significant difference in OS was observed between the two arms (P = 0.350). Adverse events were similar, except for more thrombocytopenia in the PC arm (P = 0.001)	**Limitations** Risk of Bias Assessment: 1)Selection Bias: a) Random sequence generation: Not clear b) Allocation concealment: Not clear 2) Performance Bias: Low risk. Blinding not mentioned. But, this is unlikely to have significant impact. 3) Detection Bias: Low risk. objective outcomes 4) Attrition Bias: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare carboplatin plus paclitaxel with epirubicin plus paclitaxel as neoadjuvant chemotherapy (NAC) in TNBC. **Study dates** May 2006- December 2012 **Source of funding** This study was supported by grant from Cancer Hospital, Chinese Academy of Medical Sciences (LC2010A03).	6) normal cardiac, hepatic and marrow function. **Exclusion criteria** History of invasive cancer or prior exposure to chemotherapy/ radiotherapy.				5) Selective Reporting: Unclear 6) Indirectness: None **Other information** Trial registration ID: NCT01276769
Full citation Sikov, W. M., Berry, D. A., Perou, C. M., Singh, B., Cirrincione, C. T., Tolaney, S. M., Kuzma, C. S., Pluard, T. J., Somlo, G., Port, E. R., Golshan, M., Bellon, J. R., Collyar, D., Hahn, O. M., Carey, L. A., Hudis, C. A., Winer, E. P., Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance), Journal of	**Sample size** N=433 (Intervention=221Control=212)) **Characteristics** **Inclusion criteria** 1)Operable 2) biopsy-confirmed 3)previously untreated 4) clinical stage II to III 5) noninflammatory invasive breast cancer 6) ER and PR negative 7) Adequate hematologic, renal, and hepatic function,	**Interventions** N=433 (Intervention=221, Control=212)	**Details** Control arm: paclitaxel 80mg/m^2 once per week (wP) for 12 weeks followed by doxorubicin 60mg/m^2 and cyclophosphamide 600 mg/m^2 once every 2 weeks with myeloid growth factor support (ddAC) for four cycles. Intervention arm: carboplatin at an area-under-the	**Results** Addition of carboplatin to neoadjuvant therapy (54% v 41%; P =.0029) significantly raised pCR breast/axilla	**Limitations** Risk of Bias Assessment: 1)Selection Bias: a) Random sequence generation: Not clear b) Allocation concealment: Not clear 2) Performance Bias: Low risk. Blinding not mentioned. But,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
clinical oncology, 33, 13-21, 2015 **Ref Id** 567713 **Country/ies where the study was carried out** United States **Study type** Randomized controlled trial **Aim of the study** To evaluate the impact of adding carboplatin (and/or bevacizumab)to standard neoadjuvant chemotherapy in patients with triple-negative breast cancer(TNBC). Only interested in addition of carboplatin **Study dates** May 2009 to August 2012 **Source of funding** The National Cancer Institute Cancer Therapy Evaluation Program, Genentech USA & American Recovery and Reinvestment Act to the Coalition for Cancer Cooperative Groups	normal cardiac function by echocardiogram or radionuclide ventriculogram 8) Negative pregnancy test in women of childbearing potential were required. **Exclusion criteria** Patients were excluded for grade 2. neuropathy or contraindications to treatment with bevacizumab, including uncontrolled hypertension		curve (AUC) dose of 6 once every 3 weeks for four cycles in addition to paclitaxel 80mg/m^2 once per week (wP) for 12 weeks followed by doxorubicin 60mg/m^2 and cyclophosphamide 600 mg/m^2 once every 2 weeks with myeloid growth factor support (ddAC) for four cycles.		this is unlikely to have significant impact. 3) Detection Bias: Low risk. objective outcomes 4) Attrition Bias: Low risk 5) Selective Reporting: Unclear 6) Indirectness: None **Other information** CALGB (Cancer and Leukemia Group B) 40603 trial

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Von Minckwitz, G., Schneeweiss, A., Loibl, S., Salat, C., Denkert, C., Rezai, M., Blohmer, J. U., Jackisch, C., Paepke, S., Gerber, B., Zahm, D. M., Kummel, S., Eidtmann, H., Klare, P., Huober, J., Costa, S., Tesch, H., Hanusch, C., Hilfrich, J., Khandan, F., Fasching, P. A., Sinn, B. V., Engels, K., Mehta, K., Nekljudova, V., Untch, M., Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): A randomised phase 2 trial, The Lancet Oncology, 15, 747-756, 2014 **Ref Id** 583346 **Country/ies where the study was carried out** Germany **Study type** Randomized Controlled Trial **Aim of the study**	**Sample size** 315 TNBC (158= Intervention, 157=Control) **Characteristics** Median Age for overall study sample: Intervention:48 (21–75)yrs Control: 47 (21–78)yrs Tumour grade: Grade 1 (n=8 Intervention, n=6 Control) Grade 2 (n=95 intervention, n=98 control) Grade 3 (n=192 intervention, n=189 control) **Inclusion criteria** 1) Age > 18 years 2) Women with previously untreated, unilateral or bilateral, non-metastatic primary invasive triple-negative or HER2-positive breast carcinoma 3)written informed consent. 4) Karnofsky performance status index 80 or greater	**Interventions** Intervention =Paclitaxel 80 mg/m² plus nonpegylated liposomal doxorubicin 20 mg/m², both given once a week for 18 weeks. Bevacizumab 15 mg/kg intravenously every 3 weeks simultaneously with all cycles. Carboplatin at a dose of 2·0 area under curve (AUC), once every week for 18 weeks. Dose reduced to AUC 1·5 after an interim safety analysis. The dose of carboplatin could be reduced to AUC 1·1 in case of intolerable toxic effects. Control= Paclitaxel 80 mg/m² plus nonpegylated liposomal doxorubicin 20 mg/m², both given once a week for 18 weeks. Bevacizumab 15 mg/kg intravenously every 3 weeks simultaneously with all cycles	**Details** Permitted supportive treatments were dexamethasone (2–4 mg), 5HT3 inhibitors, clemastine, ranitidine, and loperamide as standby medication for patients receiving lapatinib, but no primary prophylaxis with G-CSF was recommended. In cases of tumour progression, the study treatment was discontinued and further local or systemic treatment was permitted at the discretion of the investigator. Patients were scheduled for surgery within 21 days after last receipt of chemotherapy or after at least 28 days after the last	**Results** Of the 315 patients with triple negative breast cancer Control Group: 58 (36·9%, 95% CI 29·4–44·5) of 157 patients treated without the addition of carboplatin Intervention Group: 84 (53·2%, 54·4–60·9) of 158 patients treated with the addition of carboplatin achieved a pathological complete response (p=0·005); Using the ypT0/is ypN0 definition, 67 (42·7%, 34·9–50·4) of 157 patients and 90 (53·2%, 49·2–64·7) of 158 patients achieved a pathological complete	**Limitations** 1) TNBC is a subgroup in the main study, and segregated data is not available for all data items for this group Risk of Bias Assessment: 1)Selection Bias: a) Random sequence generation: Low risk b) Allocation concealment: High risk (not masked) 2) Performance Bias: Low risk. Although there was no blinding of participants, the outcome measures were objective, hence there is a low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the effi cacy of the addition of carboplatin to neoadjuvant therapy for triplenegative and HER2-positive breast cancer **Study dates** Screening: Aug 29, 2011, and Dec 12, 2012 **Source of funding** GlaxoSmithKline, Roche, and Teva	5) clinical stage T2–T4a-d tumours or T1c tumours with either clinical or histological stage N+ disease. 6) normal haematological, renal, liver and cardiac function **Exclusion criteria** 1) Distant disease or known or suspected cardiac disease 2) Previous thromboembolic event 3) Known haemorrhagic diathesis or coagulopathy 4) Currently active infection 5) Active peptic ulcer 6) Incomplete wound healing or unhealed bone fracture 7) Pre-existing motor or sensory neuropathy of a severity grade 2 or greater 8) Disease with a clinically significant effect on gastrointestinal function; history of abdominal fistula or gastrointestinal perforation of intra-abdominal abscess within 6 months before enrolment		bevacizumab infusion.	response (p=0·015).	3) Detection Bias: Unclear risk 4) Attrition Bias: High risk 5) Selective Reporting: Low risk 6) Indirectness: None **Other information** ClinicalTrials.gov, number NCT01426880

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	9) Severe pulmonary condition or illness 10) Major surgery within the past 28 days or anticipation of the need for major surgery during study treatment 11) Previous chemotherapy for any malignancy; Previous radiation therapy for breast cancer; and concurrent treatment with other anticancer or investigational agents.				
Full citation Ando, M, Yamauchi, H, Aogi, K, Shimizu, S, Iwata, H, Masuda, N, Yamamoto, N, Inoue, K, Ohono, S, Kuroi, K, Hamano, T, Sukigara, T, Fujiwara, Y, Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression, Breast Cancer Research and Treatment, 145, 401-9, 2014 **Ref Id** 581410	**Sample size** Total 179. Only interested in 75 TNBC participants. **Characteristics** Characteristics of TNBC subgroup not separately described. **Inclusion criteria** 1) Previously untreated, unilateral, histologically confirmed, invasive, non-inflammatory, breast carcinoma. 2) HER2-negative disease 3) Clinical stage II and IIIA 4) Age 18–70 years,	**Interventions** Intervention group: Carboplatin + Weekly Paclitaxel X 4 cycles followed by cyclophosphamide, epirubicin and 5-flourouracil X 4 cycles Control group: Weekly Paclitaxel X 4 cycles followed by cyclophosphamide, epirubicin and 5-flourouracil X 4 cycles	**Details** Intervention group: CP-CEF (four 3-week cycles of carboplatin [area under the curve 5 mg/mL/min, day 1] and wPTX [80 mg/m^2, day 1, 8, 15] followed by four 3-week cycles of CEF [500/100/500 mg/m2] Control group: P-CEF (four cycles of wPTX followed by four cycles of CEF).	**Results** Pathological complete response rate: Intervention group: 62.2% (23/37) Control group : 26.3% (10/38)	**Limitations** Risk of Bias Assessment: 1)Selection Bias: a) Random sequence generation: Low risk b) Allocation concealment: Unclear risk 2) Performance Bias: Low risk. No blinding. But, this is unlikely to have significant impact.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Japan **Study type** Randomized controlled trial **Aim of the study** To evaluate efficacy and safety of carboplatin and weekly paclitaxel (wPTX) followed by cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) as neoadjuvant chemotherapy for HER2-negative breast cancer (TNBC is a subgroup) **Study dates** March 2010 to September 2011 **Source of funding** Health and Labour Sciences Research Grants (Clinical Cancer Research), Ministry of Health, Labour and Welfare (Grant Number: MHLW, 2009 Clinical Cancer Research General-020) and the Cancer Research and Development grants, and National Cancer Center (Grant Number: 2011-A-42).	5) ECOG performance status 0–2, adequate bone marrow function , liver function , and renal function 6) Written informed consent. **Exclusion criteria** 1) History of ischemic cardiac disease 2) Patients with T4, N3, (supraclavicular lymph node), or distant metastatic disease (M1)				3) Detection Bias: Low risk. objective outcomes 4) Attrition Bias: Low risk 5) Selective Reporting: Unclear 6) Indirectness: None **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Alba, E., Chacon, J. I., Lluch, A., Anton, A., Estevez, L., Cirauqui, B., Carrasco, E., Calvo, L., Segui, M. A., Ribelles, N., Alvarez, R., Sanchez-Munoz, A., Sanchez, R., Garcia-Asenjo, J. A. L., Rodriguez-Martin, C., Escudero, M. J., Albanell, J., A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study, Breast Cancer Research and Treatment, 136, 487-493, 2012 **Ref Id** 616695 **Country/ies where the study was carried out** Spain **Study type** Multicenter Randomized Controlled Trial **Aim of the study** To investigate if the addition of carboplatin to a combination of	**Sample size** 93 **Characteristics** Age: Control arm: 47(27-70) Age: Intervention arm: 47(28-75) All patients triple negative breast cancer Histological grade I-3%, II-23%, and III-73% **Inclusion criteria** 1) Age: >18-years old 2) Histologically confirmed (by surgical or core biopsy) basal-like breast cancer, defined as ER negative, PgR negative, HER2 negative, and cytokeratin 5/6 or epidermal growth factor receptor (EGFR) positive by immunohistochemistry (IHC), were included. 3) Tumor size had <2cm cm if there was axillary involvement (pathologically confirmed).	**Interventions** Intervention arm: Control arm: (n= 46) Epirubicin+ Cyclophosphamide+Docetaxel Intervention arm: n=48) Epirubicin+ Cyclophosphamide+Docetaxel+ Carboplatin	**Details** Intervention arm: Epirubicin 90mg/m^2 + Cyclophosphamide 600mg/m^2 (q 21 days x 4 courses) followed by Docetaxel 75mg/m^2 + Carboplatin AUC 6 mg/ml/min (q 21 days x 4 courses) Control arm: Epirubicin 90mg/m^2 + Cyclophosphamide 600mg/m^2 (q 21 days x 4 courses) followed by Docetaxel 100mg/m^2 (q 21 days x 4 courses)	**Results** Pathological Complete response in Breast: Intervention arm:14 (30%) Control arm: 16(35%) pCR in Breast and Axilla : 30%(both arms) Overall clinical response: Intervention arm: 77%(65-87) Control arm: 70%(56-83)	**Limitations** Risk of Bias Assessment: 1)Selection Bias: a) Random sequence generation: low risk b) Allocation concealment: unclear risk 2) Performance Bias: Low risk. Blinding not mentioned. But, this is unlikely to have significant impact. 3) Detection Bias: Low risk. objective outcomes 4) Attrition Bias: Low risk 5) Selective Reporting: Unclear 6) Indirectness: This is basal like

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
an alkylating agent together with anthracyclines and taxanes is able to increase the efficacy in the neoadjuvant treatment context **Study dates** April 2007 - January 2010 **Source of funding** This trial was partially supported by Pfizer S.L.U	4) ECOG performance status B1, normal cardiac function, and adequate bone marrow reserve and liver and renal functions 5) Adequate contraception and a negative pregnancy test for women with child-bearing potential. **Exclusion criteria** 1) Previous treatment for the present disease 2) Previous anthracycline and/or taxane administration, have concurrent treatment with corticosteroids, selective estrogen-receptor modulators or hormonal replacement therapy 3) Inflammatory, bilateral invasive, or metastatic breast cancer 4) Severe or uncontrolled systemic disease 5) Previous history of cancer other than skin (no-melanoma), or cervix tumours adequately treated and other cancers treated more than 10 years before the study entry				breast cancer patients only **Other information** GEICAM/2006-03

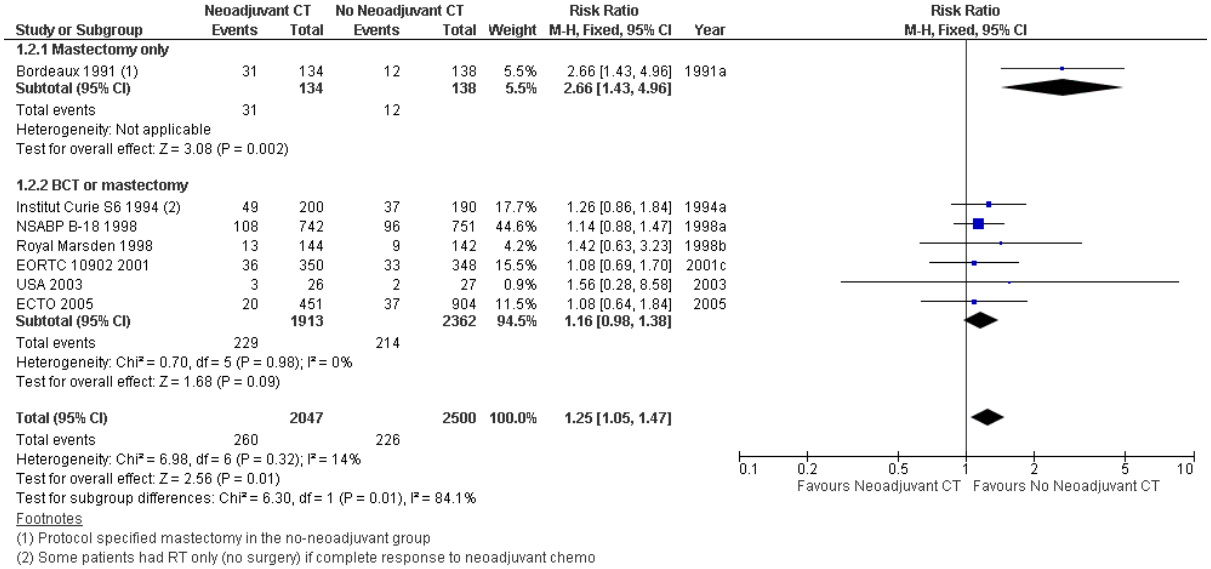
AUC, Area under curve; CALB, Cancer and Leukemia group B; CEF, Cyclophosphamide, CP, Carboplatin Paclitaxel; Epirubicin, 5-Fluorouracil; ddAC, Dose dense doxorubicin & cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EP, Epirubicin Paclitaxel; ER, Estrogen receptor; G-CSF, Granulocyte colony stimulating factor; HER-2, Human epidermal growth factor receptor 2; IHC, Immunohistochemistry; IV, intravenous; NAC, Neoadjuvant chemotherapy; OS, Overall survival; pCR, Pathological complete response; PR, Progesterone receptor; RFS, Relapse free survival; TNBC, Triple negative breast cancer; wP, weekly Paclitaxel

Appendix E – Forest plots

Forest plots for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

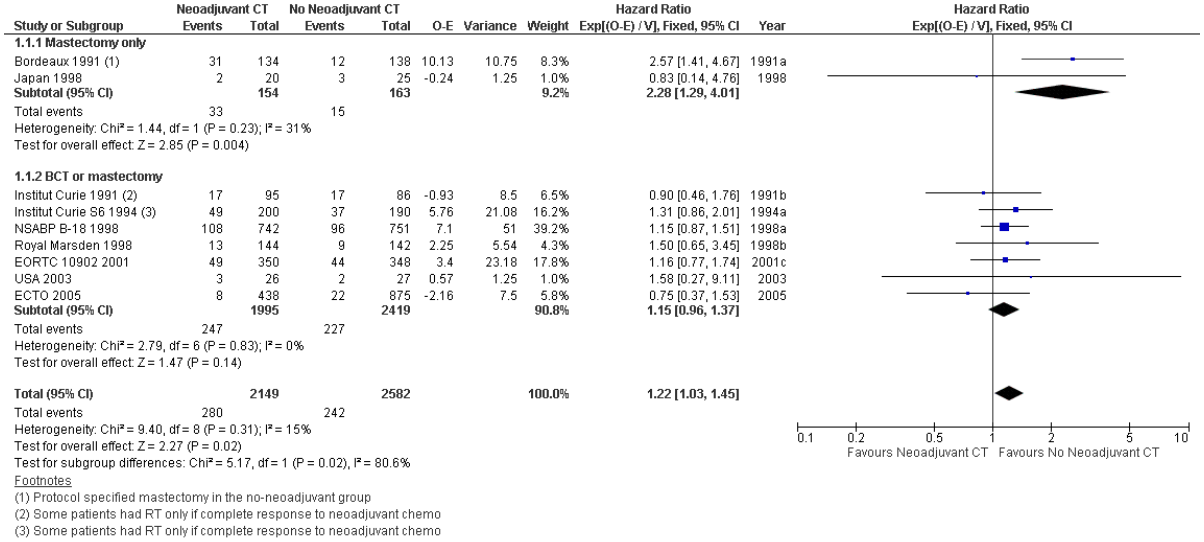
Comparison 1. Anthracycline-containing neoadjuvant chemotherapy versus no neoadjuvant chemotherapy

Figure 5: Local recurrence at median follow up 8 to 16 years



Footnotes
(1) Protocol specified mastectomy in the no-neoadjuvant group
(2) Some patients had RT only (no surgery) if complete response to neoadjuvant chemo

Figure 6: Local recurrence free survival at median follow up 5 to 16 years



Footnotes

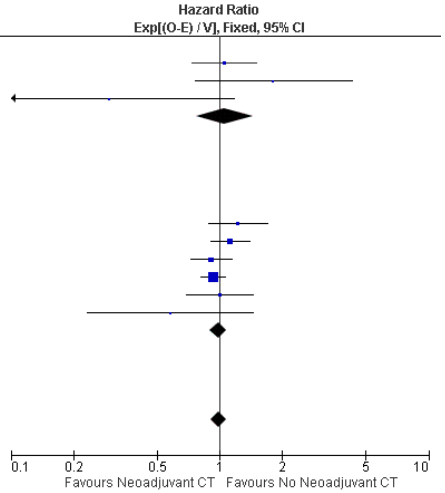
(1) Protocol specified mastectomy in the no-neoadjuvant group

(2) Some patients had RT only if complete response to neoadjuvant chemo

(3) Some patients had RT only if complete response to neoadjuvant chemo

Figure 7: Disease-free survival at median follow up 2 to 16 years

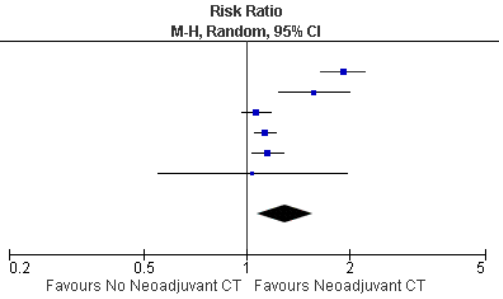
Study or Subgroup	Neoadjuvant CT Events	Neoadjuvant CT Total	No Neoadjuvant CT Events	No Neoadjuvant CT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.3.1 Mastectomy only								
Bordeaux 1991	57	134	54	138	1.53	30.86	6.5%	1.05 [0.74, 1.50]
Deo 2003	12	50	9	51	3.04	5.14	1.1%	1.81 [0.76, 4.29]
Japan 1998	2	20	10	25	-2.49	2.05	0.4%	0.30 [0.08, 1.17]
Subtotal (95% CI)		**204**		**214**			**8.0%**	**1.06 [0.77, 1.45]**
Total events	71		73					
Heterogeneity: Chi² = 4.78, df = 2 (P = 0.09); I² = 58%								
Test for overall effect: Z = 0.34 (P = 0.74)								
1.3.2 BCT or mastectomy								
ECTO 2005 (1)	0	451	0	451	7.18	36.08	7.6%	1.22 [0.88, 1.69]
EORTC 10902 2001	172	350	160	348	9.53	84.1	17.7%	1.12 [0.90, 1.39]
Institut Curie S6 1994	82	200	86	190	-6.83	73.38	15.4%	0.91 [0.72, 1.15]
NSABP B-18 1998	410	742	434	751	-15.3	210.83	44.3%	0.93 [0.81, 1.06]
Royal Marsden 1998	42	144	41	142	0	29.2	6.1%	1.00 [0.70, 1.44]
USA 2003	8	26	11	27	-2.53	4.63	1.0%	0.58 [0.23, 1.44]
Subtotal (95% CI)		**1913**		**1909**			**92.0%**	**0.98 [0.89, 1.08]**
Total events	714		732					
Heterogeneity: Chi² = 5.49, df = 5 (P = 0.36); I² = 9%								
Test for overall effect: Z = 0.38 (P = 0.70)								
Total (95% CI)		**2117**		**2123**			**100.0%**	**0.99 [0.90, 1.08]**
Total events	785		805					
Heterogeneity: Chi² = 10.46, df = 8 (P = 0.23); I² = 24%								
Test for overall effect: Z = 0.27 (P = 0.79)								
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.67), I² = 0%								



Footnotes
(1) Event rate not reported

Figure 8: Breast conserving therapy rate

Study or Subgroup	Neoadjuvant CT Events	Neoadjuvant CT Total	No Neoadjuvant CT Events	No Neoadjuvant CT Total	Weight	Risk Ratio M-H, Random, 95% CI
Bordeaux 1991 (1)	84	134	0	138		Not estimable
ECTO 2005	284	451	148	451	18.5%	1.92 [1.65, 2.23]
EORTC 10902 2001	122	350	77	348	15.6%	1.58 [1.23, 2.01]
Institut Curie S6 1994	164	200	146	190	19.8%	1.07 [0.96, 1.18]
NSABP B-18 1998	517	760	458	763	20.3%	1.13 [1.05, 1.22]
Royal Marsden 1998	132	149	111	144	19.7%	1.15 [1.03, 1.28]
USA 2003	11	26	11	27	6.2%	1.04 [0.55, 1.97]
Total (95% CI)		**1936**		**1923**	**100.0%**	**1.30 [1.07, 1.57]**
Total events	1230		951			
Heterogeneity: Tau² = 0.04; Chi² = 57.67, df = 5 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 2.68 (P = 0.007)						



Footnotes
(1) Protocol specified mastectomy in the no-neoadjuvant group

Figure 9: Overall survival at at median follow up 2 to 16 years

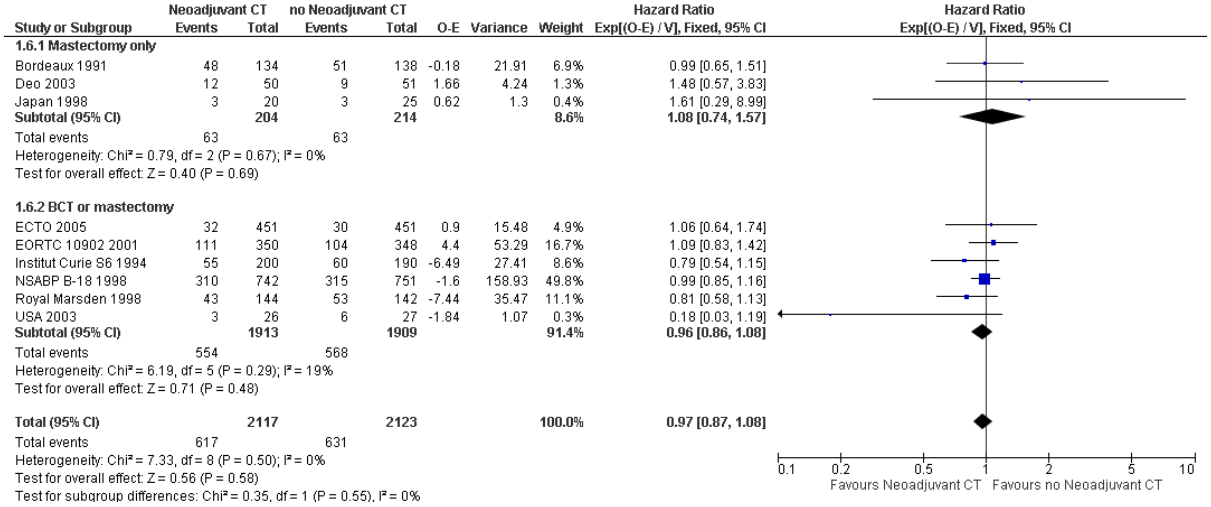
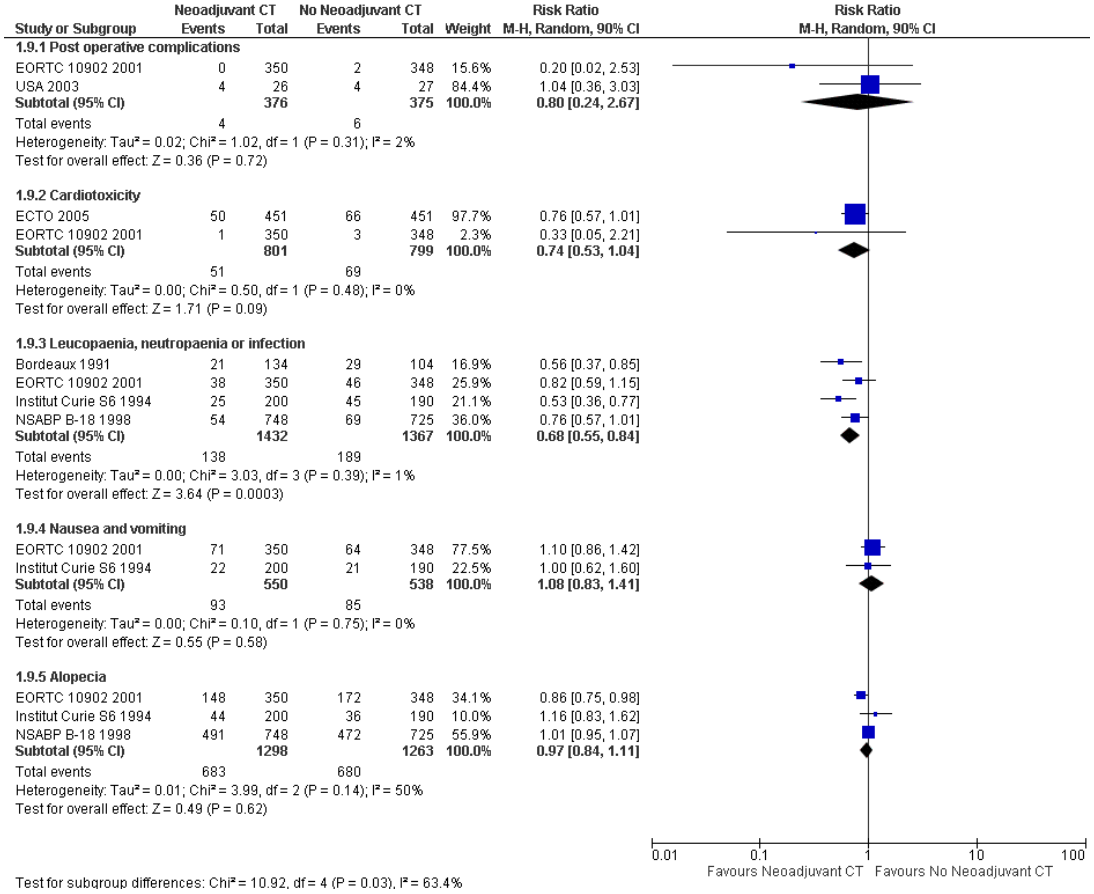


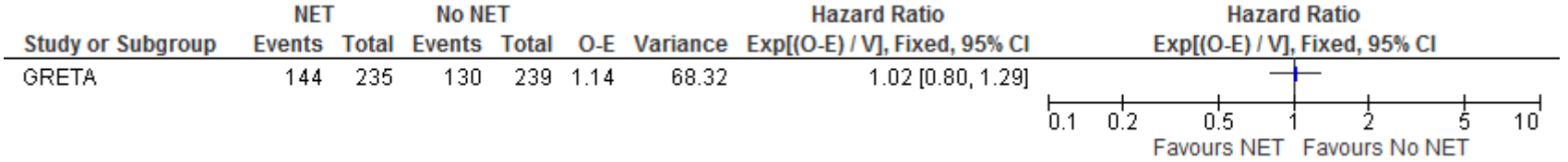
Figure 10: Adverse events in the post-operative period



Forest plots for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

Comparison 1. Neoadjuvant endocrine therapy versus no neoadjuvant endocrine therapy

Figure 11: Overall survival at 6.7 year follow-up



Comparison 2. Neoadjuvant endocrine therapy versus neoadjuvant chemotherapy

Figure 12: Breast conservation rates

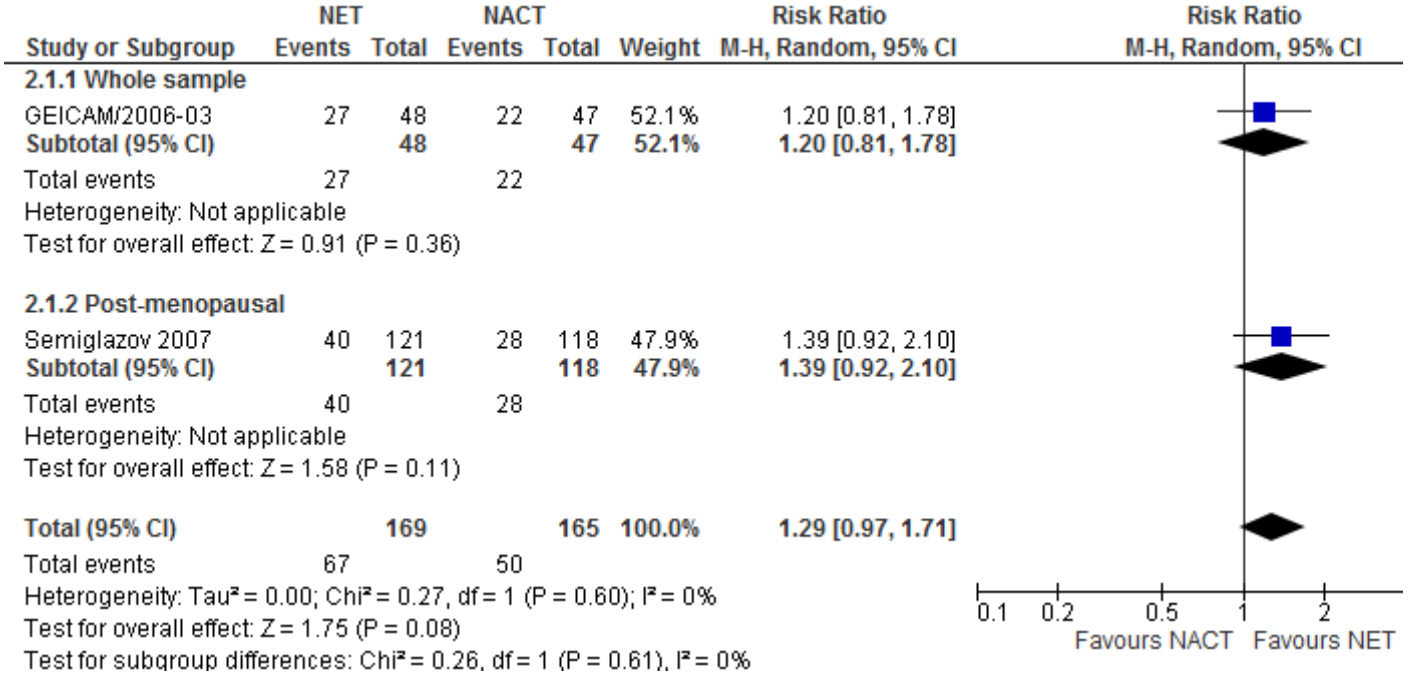


Figure 13: Changes in tumour size – clinical response

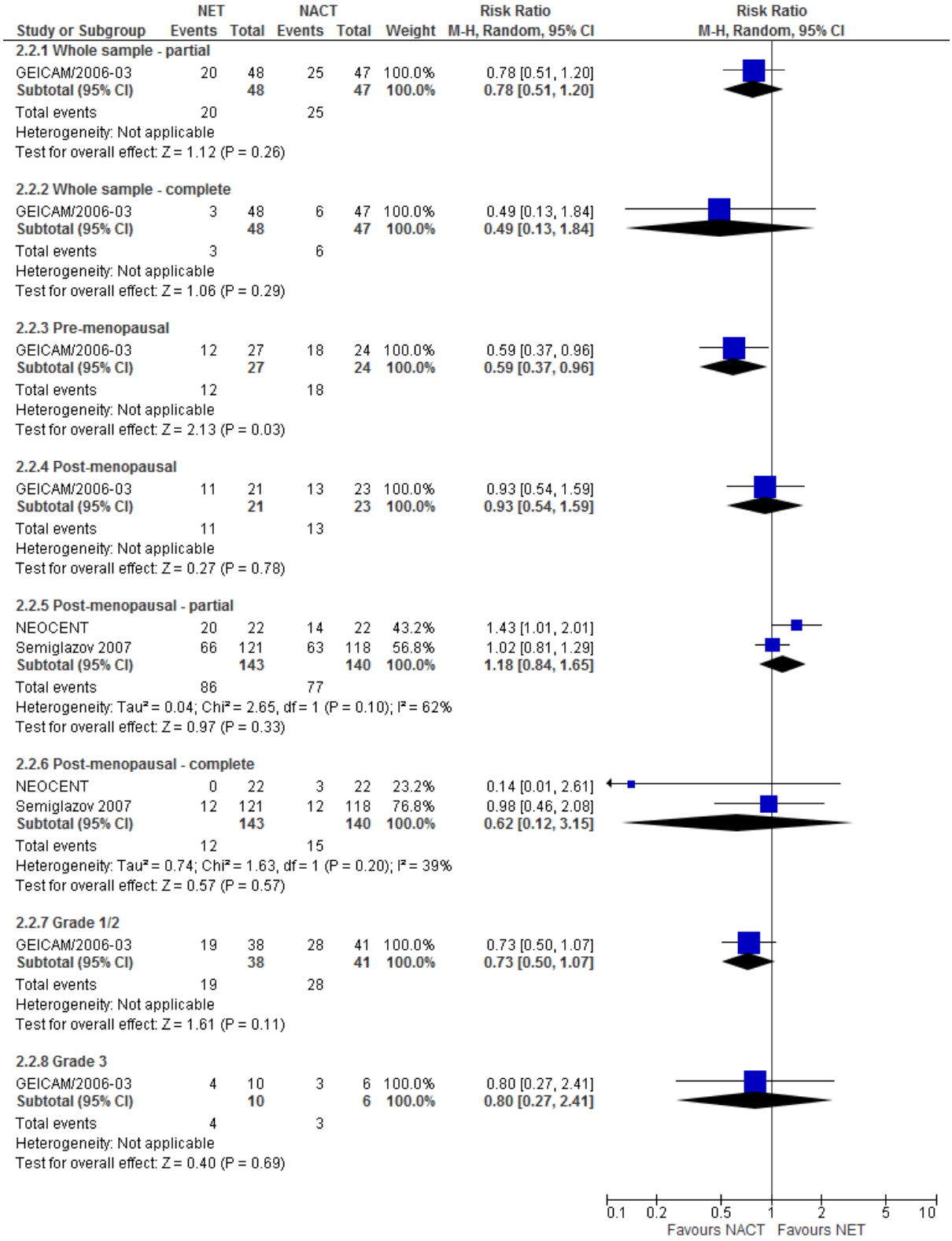


Figure 14: Changes in tumour size – radiological response

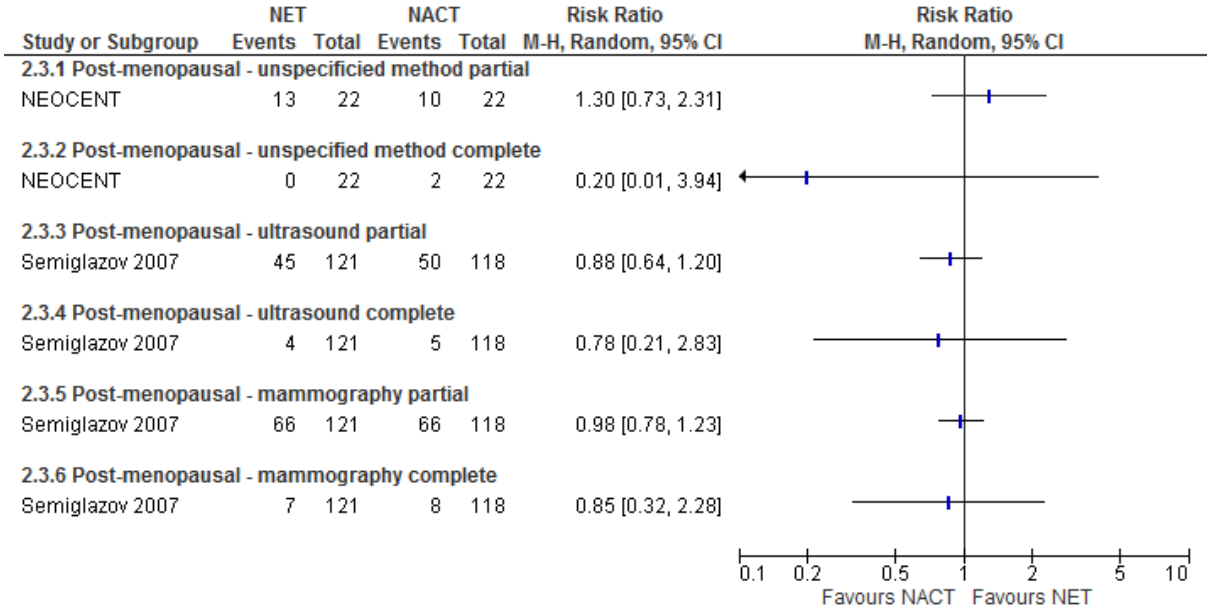
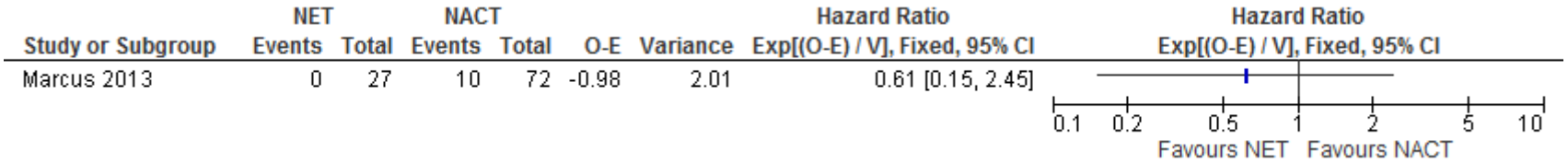


Figure 15: Changes in tumour size – overall survival at 4 year follow-up



Forest plots for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

Comparison 1. Postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy versus no radiotherapy

Figure 16: Locoregional recurrence at 4 to 10 year follow

	Post-mastectomy RT		No RT					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
Abdel-Wahab 1998	3	42	4	13	-2.5	1.26	4.6%	0.14 [0.02, 0.79]	
Garg 2007	18	80	10	27	-7.56	5.28	19.4%	0.24 [0.10, 0.56]	
Huang 2004	60	542	29	134	-14.64	14.16	52.1%	0.36 [0.21, 0.60]	
Meattini 2014	14	98	12	72	-1.44	6.46	23.8%	0.80 [0.37, 1.73]	
Total (95% CI)		**762**		**246**			**100.0%**	**0.38 [0.26, 0.56]**	
Total events	95		55						

Heterogeneity: Chi² = 6.08, df = 3 (P = 0.11); I² = 51%

Test for overall effect: Z = 5.02 (P < 0.00001)

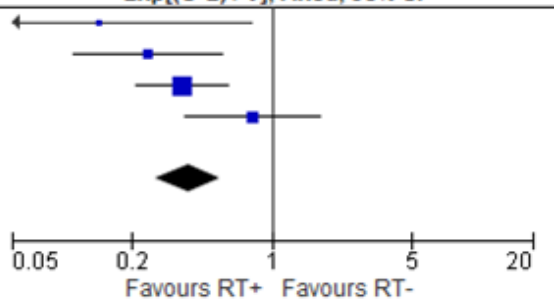


Figure 17: Locoregional recurrence at 5 to 10 year follow: T stage subgroups

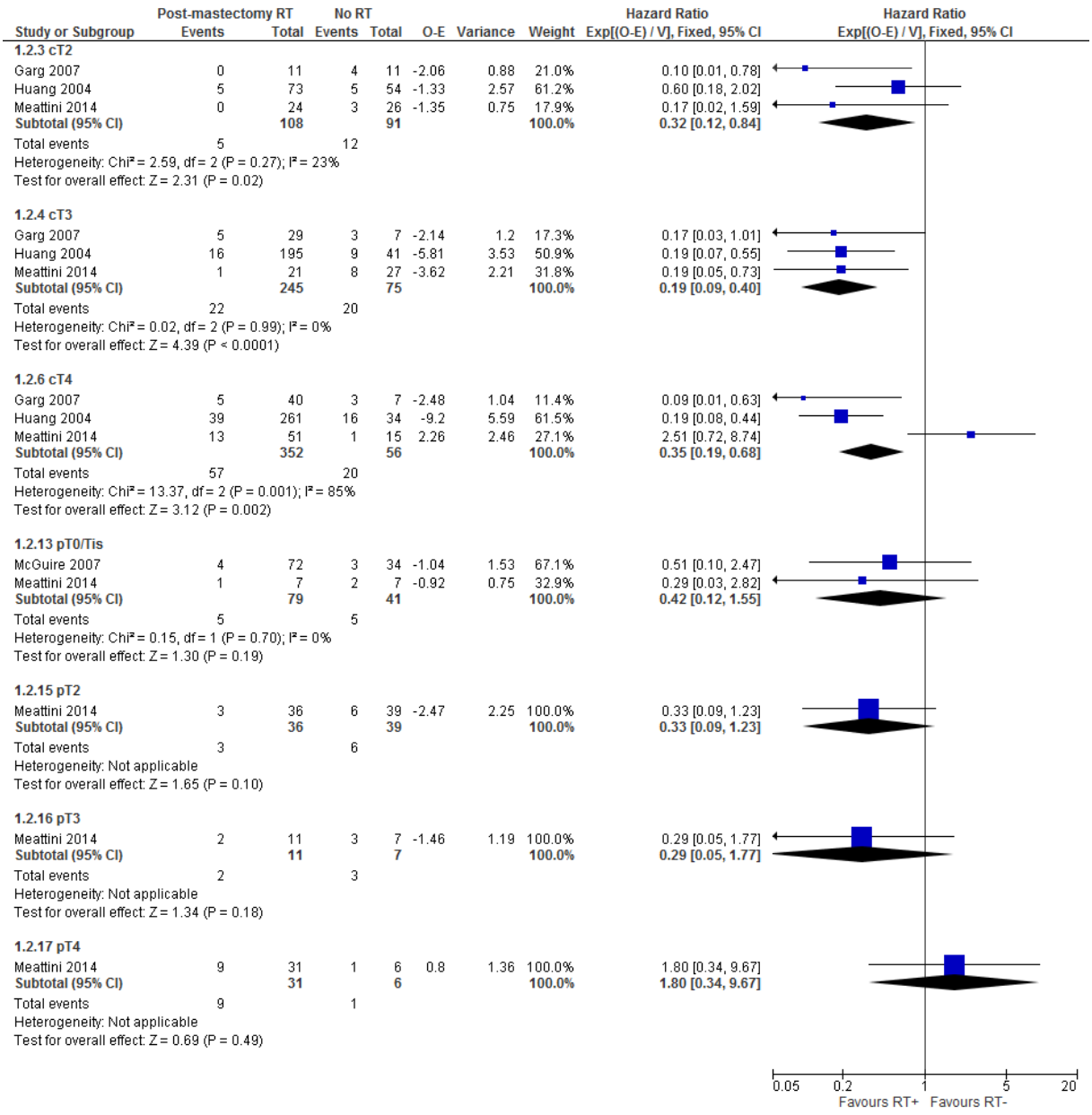


Figure 18: Locoregional recurrence at 5 to 10 year follow: N stage subgroups

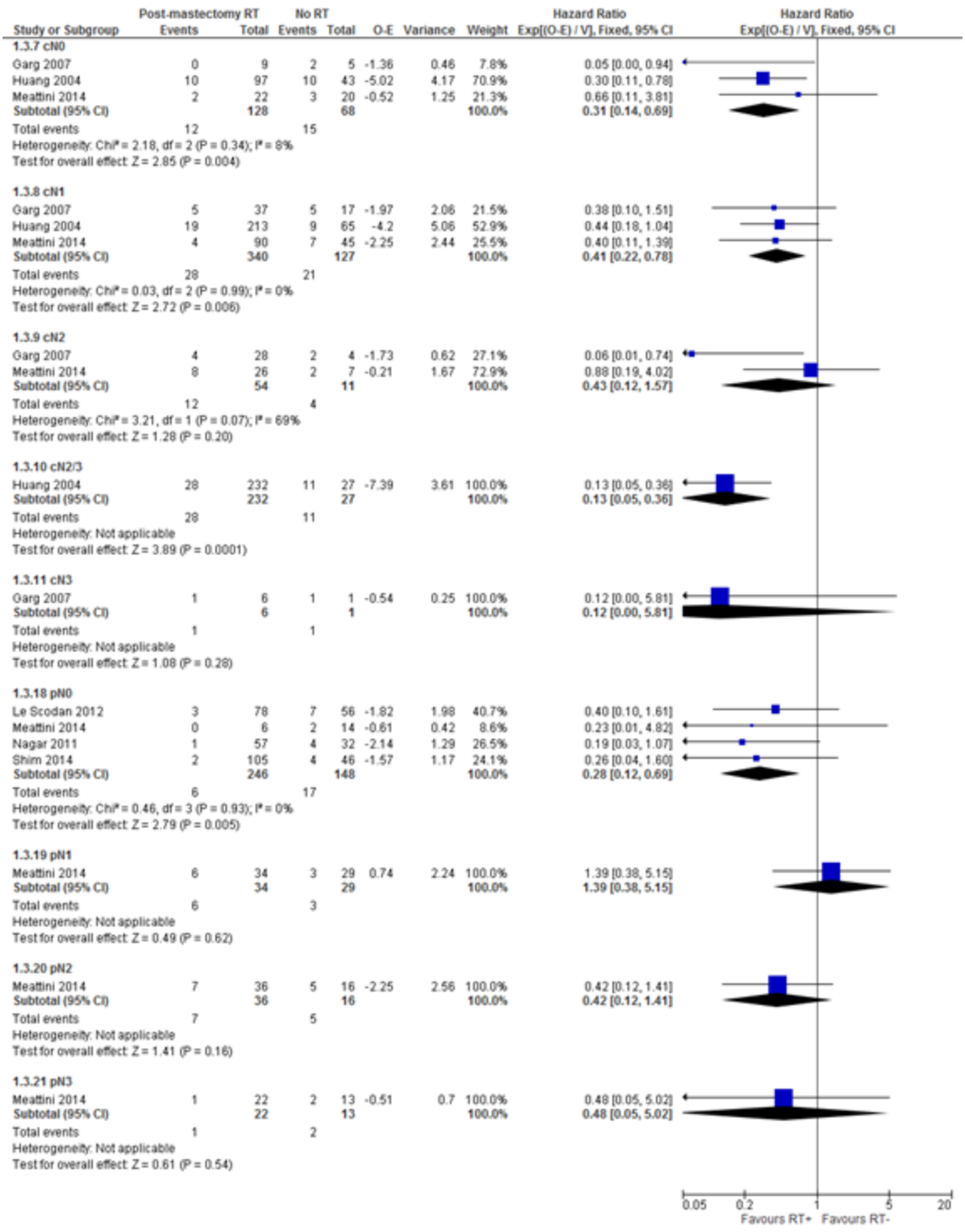


Figure 19: Locoregional recurrence at 5 year follow: T & N stage combined subgroups

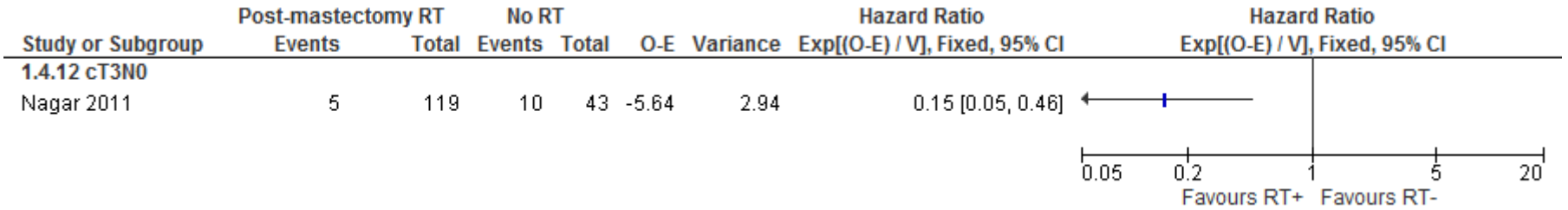


Figure 20: Disease-free survival at 5 to 10 year follow-up

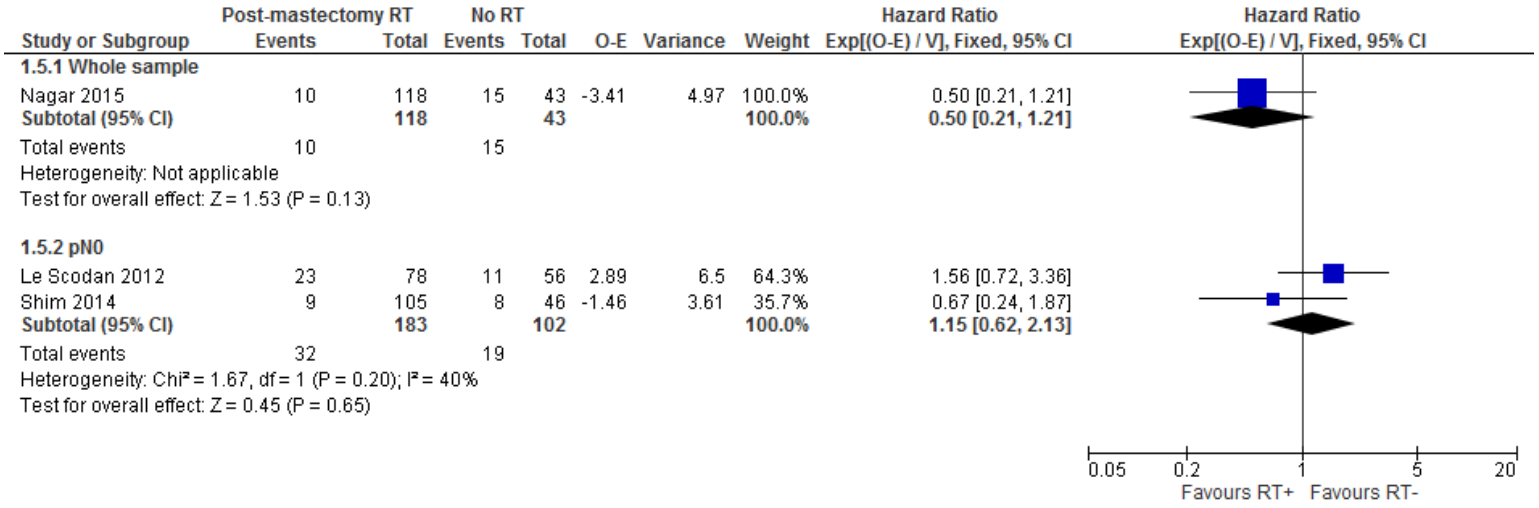


Figure 21: Overall survival at 4 to 10 year follow-up

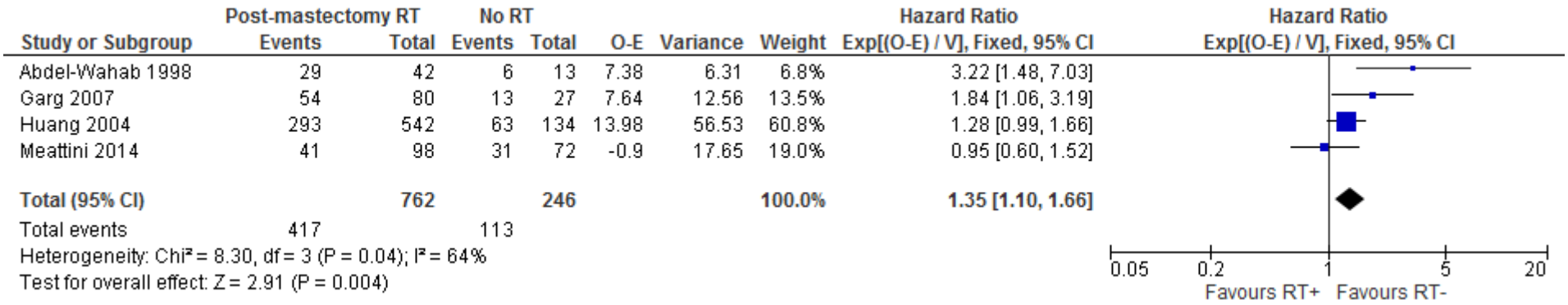


Figure 22: Overall survival at 3.25 to 10 year follow-up: T stage subgroups

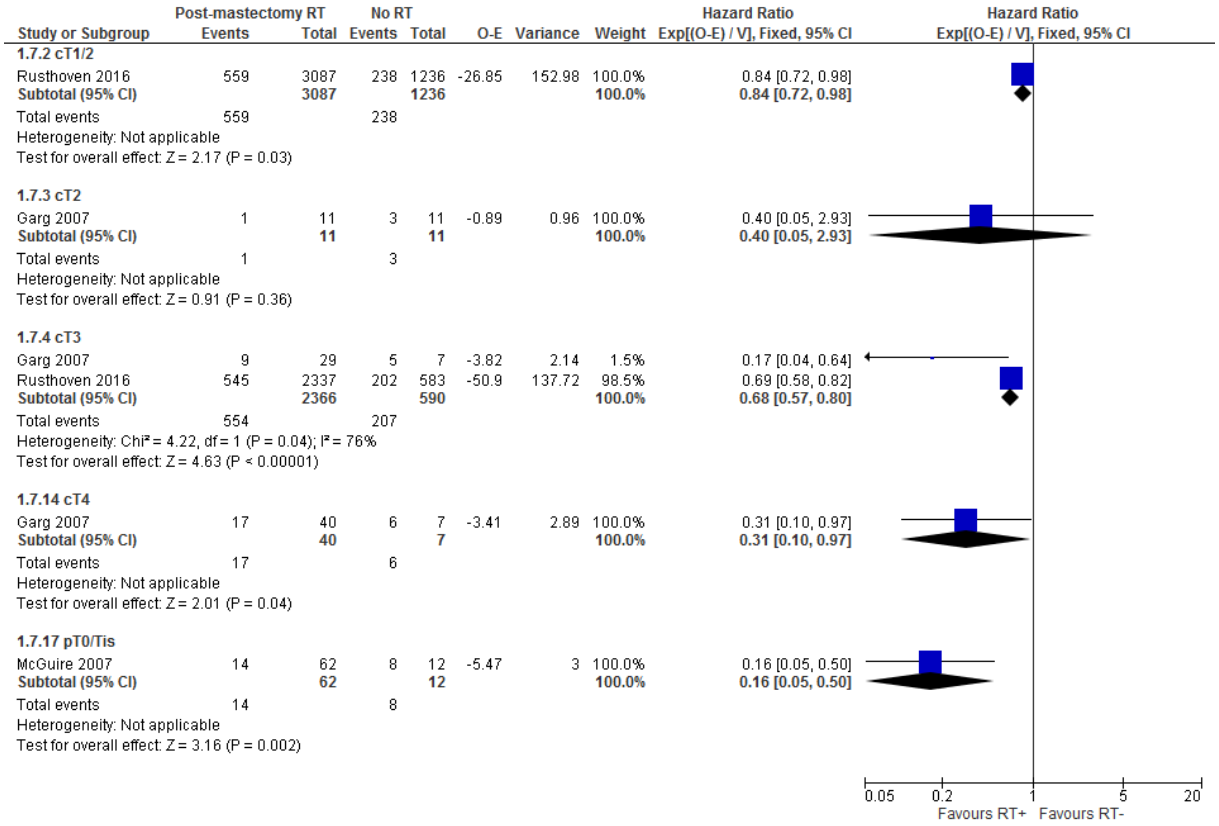


Figure 23: Overall survival at 3.25 to 10 year follow-up: N stage subgroups

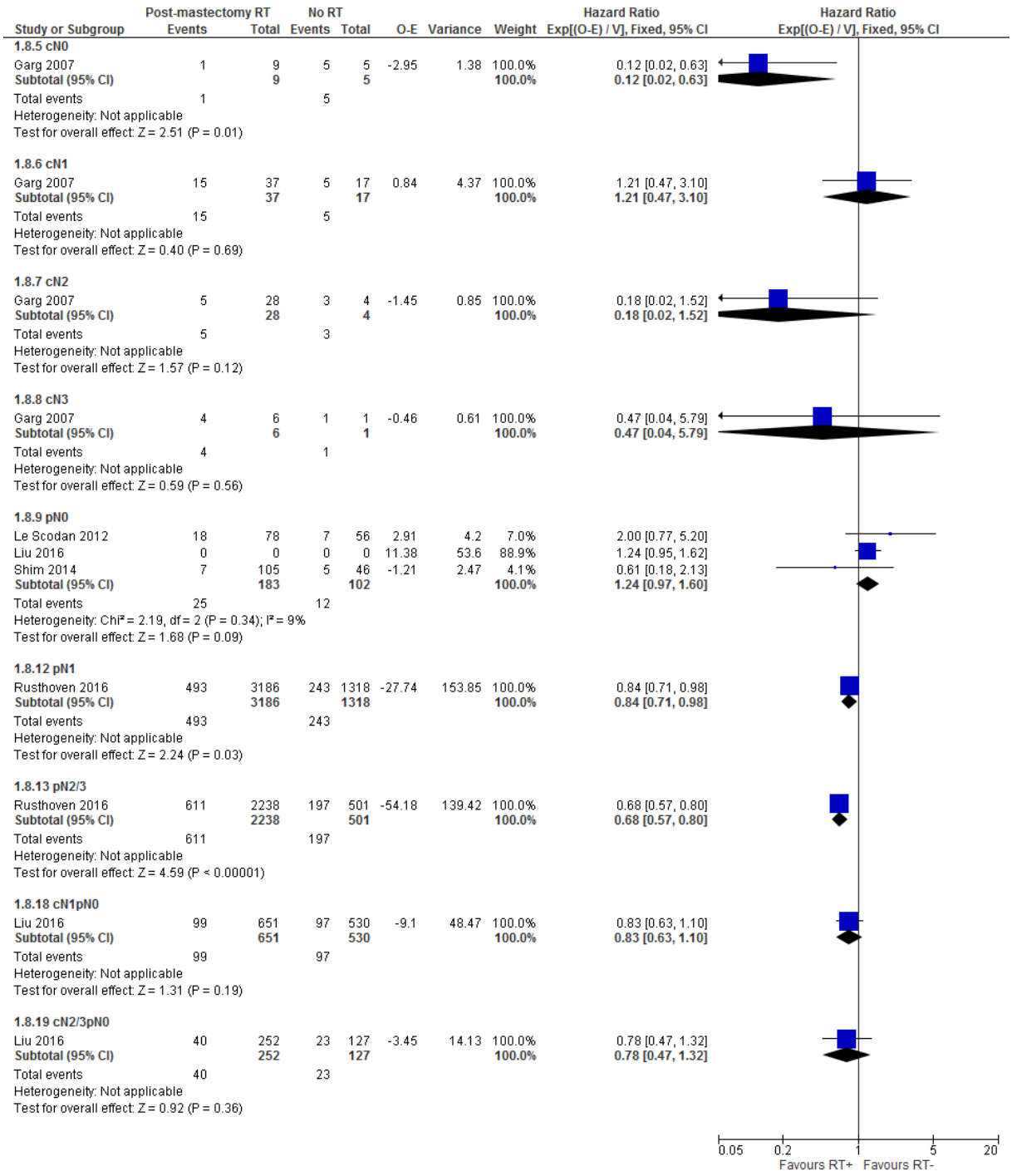
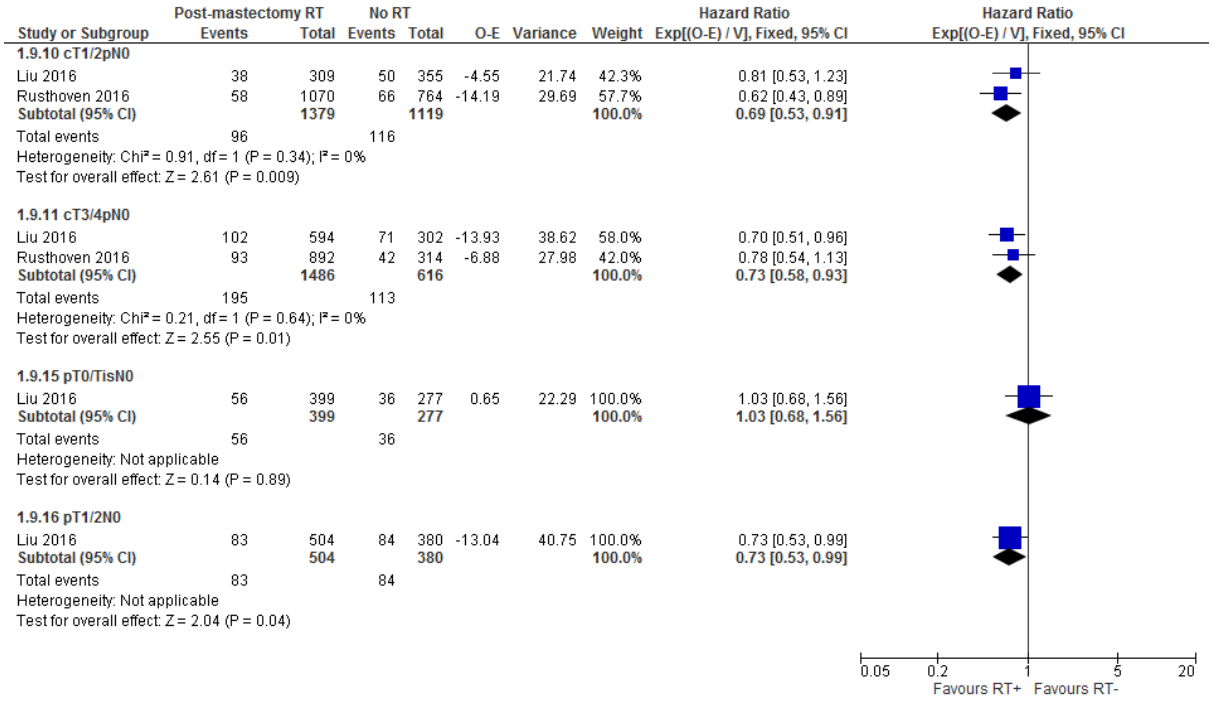


Figure 24: Overall survival at 3.25 to 5 year follow-up: T & N stage combined subgroups



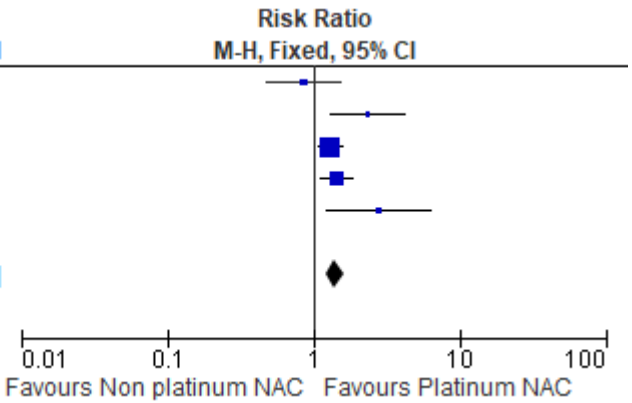
Forest plots for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

Comparison 1. Platinum containing regimen vs non-platinum containing regimen in adults with triple negative invasive breast cancer

Figure 25: Pathological response rate at surgery

Study or Subgroup	Platinum NAC Events	Platinum NAC Total	Non Platinum NAC Events	Non Platinum NAC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alba 2012	14	47	16	46	8.5%	0.86 [0.47, 1.55]
Ando 2014	23	37	10	38	5.2%	2.36 [1.31, 4.25]
Sikov 2014	133	221	98	212	52.5%	1.30 [1.09, 1.56]
Von minckwitz 2014	84	158	58	157	30.5%	1.44 [1.12, 1.85]
Zhang 2016	18	47	6	44	3.3%	2.81 [1.23, 6.42]
Total (95% CI)		**510**		**497**	**100.0%**	**1.41 [1.23, 1.62]**
Total events	272		188			

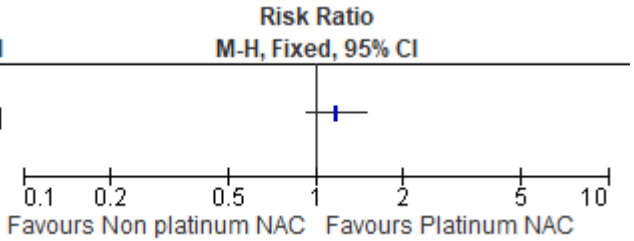
Heterogeneity: Chi² = 9.13, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 4.90 (P < 0.00001)



CI: Confidence interval; NAT: neoadjuvant chemotherapy; pCR: pathological complete response rate

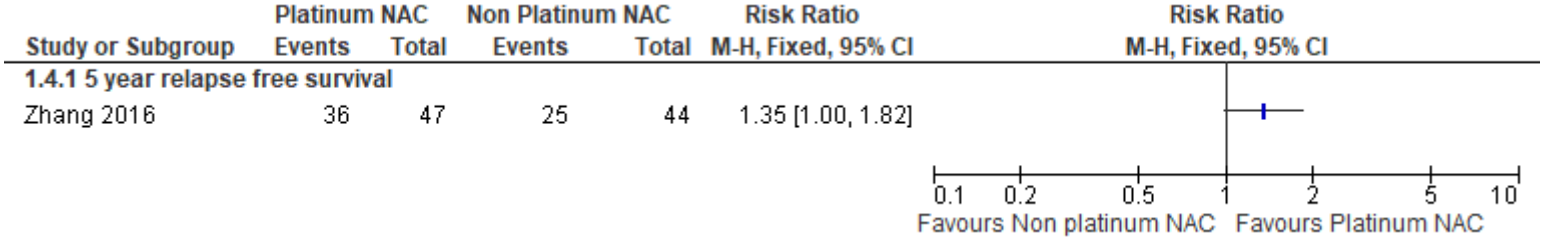
Figure 26: Overall 5 year Survival at 55 months follow up

Study or Subgroup	Platinum NAC Events	Platinum NAC Total	Non Platinum NAC Events	Non Platinum NAC Total	Risk Ratio M-H, Fixed, 95% CI
1.2.1 5 year overall survival					
Zhang 2016	39	47	31	44	1.18 [0.93, 1.48]



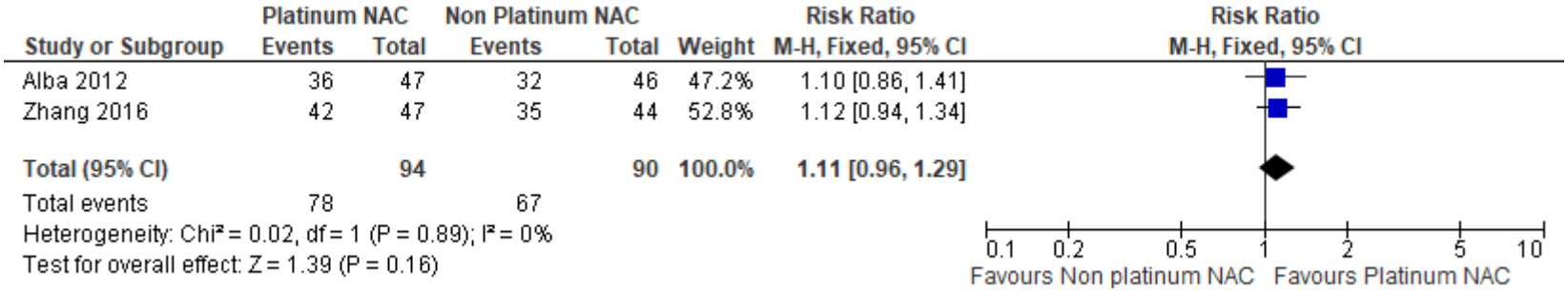
CI: Confidence interval; NAC: neoadjuvant chemotherapy; OS: Overall survival

Figure 27: 5 year disease free survival at 55 months follow up



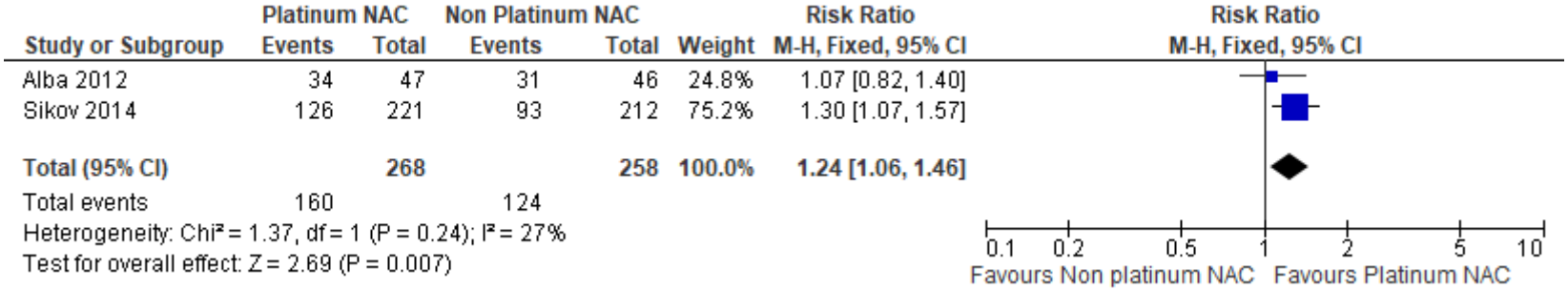
CI: Confidence interval; DFS: Disease free survival; NAC: neoadjuvant chemotherapy

Figure 28: Overall response rate following surgery



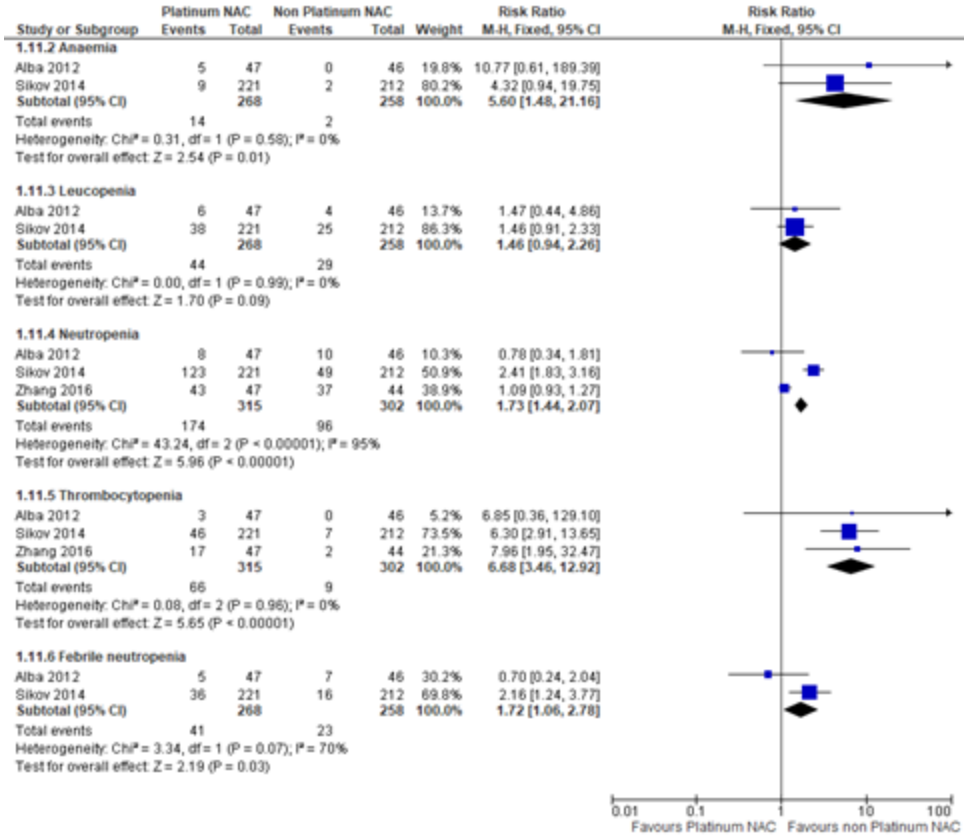
CI: Confidence interval; NAC: neoadjuvant chemotherapy; ORR: Overall response rate

Figure 29: Breast conservation rate at surgery



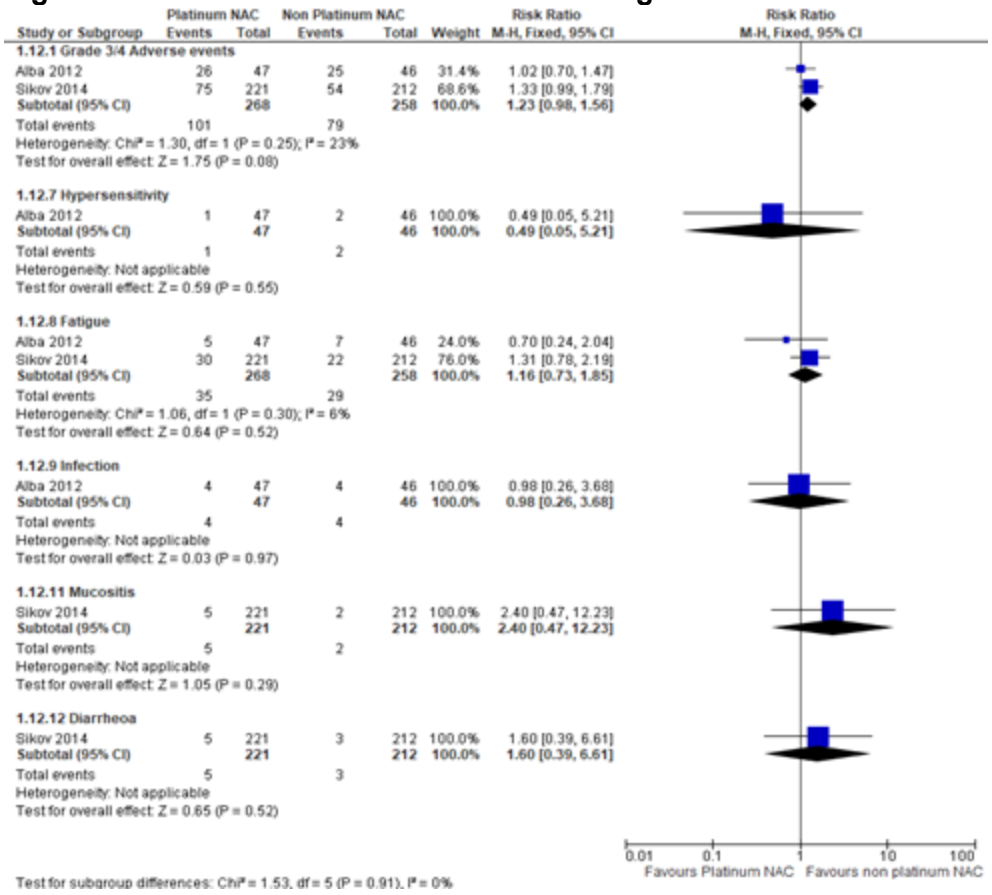
CI: Confidence interval; NAC: neoadjuvant chemotherapy

Figure 30: Treatment-related morbidities - haematological



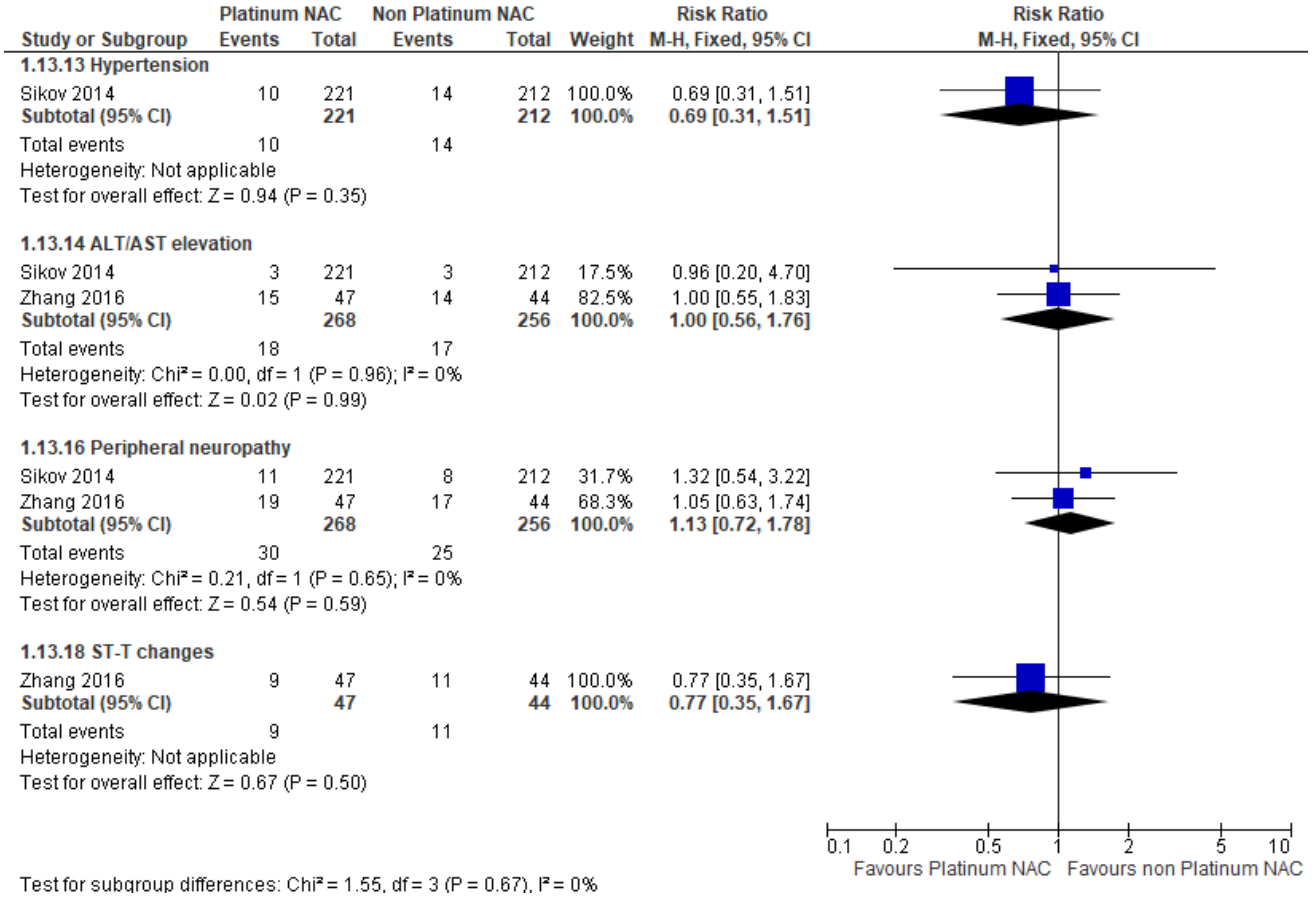
CI: Confidence interval NAC: neoadjuvant chemotherapy

Figure 31: Treatment related morbidities - general



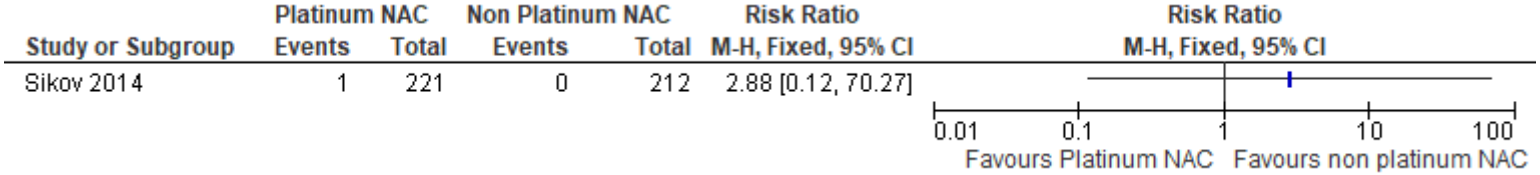
CI: Confidence interval NAC: neoadjuvant chemotherapy

Figure 32: Treatment related morbidities - systemic



CI: Confidence interval; NAC: neoadjuvant chemotherapy;

Figure 33: Treatment related mortality



CI: Confidence interval; NAC: neoadjuvant chemotherapy

Appendix F – GRADE tables

GRADE tables for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

Table 19: Comparison 1. Anthracycline-containing neoadjuvant chemotherapy versus no neoadjuvant chemotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	Relative (95% CI)	Absolute	Quality	Importance
Local recurrence (follow-up 8 to 16 years)												
6[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	229/1913 (12%)	214/2362 (9.1%)	HR 1.16 (0.98 to 1.38)	14 more per 1000 (from 2 fewer to 34 more)	HIGH	CRITICAL
Locoregional recurrence free survival (follow-up 5 to 16 years)												
7[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	247/1995 (12.4%)	227/2419 (9.4%)	HR 1.15 (0.96 to 1.37)	13 more per 1000 (from 4 fewer to 32 more)	HIGH	CRITICAL
DFS (follow-up 2 to 16 years)												
9	Randomised trials	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	None	785/2117 (37.1%)	805/2123 (37.9%)	HR 0.99 (0.9 to 1.08)	3 fewer per 1000	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	Relative (95% CI)	Absolute		
		of bias								(from 30 fewer to 23 more)		
Breast-conservation therapy rate (follow-up post-op)												
6	Randomised trials	No serious risk of bias	Very serious[3]	No serious indirectness	No serious imprecision	None	1230/1936 (63.5%)	951/1923 (49.5%)	RR 1.3 (1.07 to 1.57)	148 more per 1000 (from 35 more to 282 more)	LOW	IMPORTANT
Pathologic complete response after neoadjuvant chemotherapy (follow-up post-op)												
4	Observational[4] studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	230/1765 (13%)	-	-	Not Range 4% to 23%	LOW	IMPORTANT
OS (follow-up 2 to 16 years)												
9	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	617/2117 (29.1%)	631/2123 (29.7%)	HR 0.97 (0.87 to 1.08)	7 fewer per 1000 (from 33 fewer	HIGH	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	Relative (95% CI)	Absolute		
										to 20 more)		
Objective response after neoadjuvant chemotherapy (follow-up post-op)												
7	Observational[4]studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1437/2173 (66.1%)	-	-	Not pooled	LOW	IMPORTANT
Post-operative complications (follow-up post-op)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5,6]	None	4/376 (1.1%)	6/375 (1.6%)	RR 0.71 (0.23 to 2.20)	5 fewer per 1000 (from 12 fewer to 19 more)	LOW	NOT IMPORTANT
Cardiotoxicity (during or post-chemotherapy)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2,6]	None	51/801 (6.4%)	69/799 (8.6%)	RR 0.74 (0.53 to 1.04)	22 fewer per 1000 (from 41 fewer to 3 more)	LOW	NOT IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	Relative (95% CI)	Absolute		
Leucopaenia, neutropaenia or infection (during or post-chemotherapy)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	138/1432 (9.6%)	189/1367 (13.8%)	RR 0.69 (0.56 to 0.84)	43 fewer per 1000 (from 22 fewer to 61 fewer)	HIGH	NOT IMPORTANT
Nausea or vomiting (during or post-chemotherapy)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2,6]	None	93/550 (16.9%)	85/538 (15.8%)	RR 1.08 (0.82 to 1.41)	13 more per 1000 (from 28 fewer to 65 more)	LOW	NOT IMPORTANT
Alopecia (during or post-chemotherapy)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	683/1298 (52.6%)	680/1263 (53.8%)	RR 0.98 (0.91 to 1.05)	11 fewer per 1000 (from 48 fewer to 27 more)	HIGH	NOT IMPORTANT

CI, confidence interval; HR, hazard ratio; OS, overall survival; RR, risk ratio
[1] Excluding mastectomy only trials – due to serious heterogeneity
[2] 95% confidence interval crosses boundary for no effect (1) and one minimally important difference (0.8 and 1.25) based on GRADE default values
[3] Very serious heterogeneity, I-squared = 91%; random effects model used - no pre-specified subgroups accounted for heterogeneity.
[4] Study design was observational for this outcome – as data only came from the neoadjuvant arm
[5] 95% confidence interval crosses boundary for no effect (1) and both minimally important differences (0.8 and 1.25) based on GRADE default values
[6] < 300 events

GRADE tables for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

Table 20: Clinical evidence profile: Comparison 1. Neoadjuvant endocrine therapy versus no neoadjuvant endocrine therapy)

Quality assessment							No of patients		Effect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NET	No NET	Relative (95% CI)	Absolute	Quality		Importance
Overall survival (6.7 year follow-up)													
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	None	144/235 (61.3%)	130/239 (54.4%)	HR 1.02 (0.8 to 1.29)	7 more per 1000 (from 78 fewer to 93 more)	LOW		IMPORTANT

CI, confidence interval; HR, hazard ratio; NET, neoadjuvant endocrine therapy
[1] Proportion of patients ER+ unknown - only assessed in 24%
[2] <300 events

Table 21: Clinical evidence profile: Comparison 2. Neoadjuvant endocrine therapy versus neoadjuvant chemotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NET	NACT	Relative (95% CI)	Absolute	Quality	Importance
Breast conservation rates - Whole sample												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	27/48 (56.3%)	22/47 (46.8%)	RR 1.2 (0.81 to 1.78)	94 more per 1000 (from 89 fewer to 365 more)	LOW	CRITICAL
Breast conservation rates - Post-menopausal												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[1]	None	40/121 (33.1%)	28/118 (23.7%)	RR 1.39 (0.92 to 2.1)	93 more per 1000 (from 19 fewer to 261 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NET	NACT	Relative (95% CI)	Absolute		
Changes in tumour size - Clinical response - Whole sample - partial												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	20/48 (41.7%)	25/47 (53.2%)	RR 0.78 (0.51 to 1.2)	117 fewer per 1000 (from 261 fewer to 106 more)	LOW	CRITICAL
Changes in tumour size - Clinical response - Whole sample - complete												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	3/48 (6.3%)	6/47 (12.8%)	RR 0.49 (0.13 to 1.84)	65 fewer per 1000 (from 111 fewer to 107 more)	LOW	CRITICAL
Changes in tumour size - Clinical response - Pre-menopausal												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	None	12/27 (44.4%)	18/24 (75%)	RR 0.59 (0.37 to 0.96)	308 fewer per 1000 (from 30 fewer to 472 fewer)	MODERATE	CRITICAL
Changes in tumour size - Clinical response - Post-menopausal												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	11/21 (52.4%)	13/23 (56.5%)	RR 0.93 (0.54 to 1.59)	40 fewer per 1000 (from 260 fewer to 333 more)	LOW	CRITICAL
Changes in tumour size - Clinical response - Post-menopausal - partial												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[6]	Very serious[1]	None	86/143 (60.1%)	77/140 (55%)	RR 1.18 (0.84 to 1.65)	99 more per 1000 (from 88 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NET	NACT	Relative (95% CI)	Absolute	Quality	Importance
										357 more)		
Changes in tumour size - Clinical response - Post-menopausal - complete												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[6]	Very serious[4]	None	12/143 (8.4%)	15/140 (10.7%)	RR 0.62 (0.12 to 3.15)	41 fewer per 1000 (from 94 fewer to 230 more)	VERY LOW	CRITICAL
Changes in tumour size - Clinical response - Grade 1/2												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	19/38 (50%)	28/41 (68.3%)	RR 0.73 (0.5 to 1.07)	184 fewer per 1000 (from 341 fewer to 48 more)	LOW	CRITICAL
Changes in tumour size - Clinical response - Grade 3												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	4/10 (40%)	3/6 (50%)	RR 0.8 (0.27 to 2.41)	100 fewer per 1000 (from 365 fewer to 705 more)	LOW	CRITICAL
Changes in tumour size - Radiological response - Post-menopausal - unspecified method partial												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	13/22 (59.1%)	10/22 (45.5%)	RR 1.3 (0.73 to 2.31)	136 more per 1000 (from 123 fewer to 595 more)	LOW	CRITICAL
Changes in tumour size - Radiological response - Post-menopausal - unspecified method complete												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NET	NACT	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	0/22 (0%)	2/22 (9.1%)	RR 0.2 (0.01 to 3.94)	73 fewer per 1000 (from 90 fewer to 267 more)	LOW	CRITICAL
Changes in tumour size - Radiological response - Post-menopausal - ultrasound partial												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	45/121 (37.2%)	50/118 (42.4%)	RR 0.88 (0.64 to 1.2)	51 fewer per 1000 (from 153 fewer to 85 more)	VERY LOW	CRITICAL
Changes in tumour size - Radiological response - Post-menopausal - ultrasound complete												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[4]	None	4/121 (3.3%)	5/118 (4.2%)	RR 0.78 (0.21 to 2.83)	9 fewer per 1000 (from 33 fewer to 78 more)	VERY LOW	CRITICAL
Changes in tumour size - Radiological response - Post-menopausal - mammography partial												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	66/121 (54.5%)	66/118 (55.9%)	RR 0.98 (0.78 to 1.23)	11 fewer per 1000 (from 123 fewer to 129 more)	VERY LOW	CRITICAL
Changes in tumour size - Radiological response - Post-menopausal - mammography complete												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[4]	None	7/121 (5.8%)	8/118 (6.8%)	RR 0.85 (0.32 to 2.28)	10 fewer per 1000 (from 46 fewer to 87 more)	VERY LOW	CRITICAL
Overall survival (non-RCT) – post-menopausal (4 year follow-up)												
1	Observational studies	Serious[7]	No serious inconsistency	No serious indirectness	Serious[5]	None	0/27 (0%)	10/72 (13.9%)	HR 0.61 (0.15 to 2.45)	52 fewer per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NET	NACT	Relative (95% CI)	Absolute	Quality	Importance
										117 fewer to 168 more)		

CI, confidence interval; ER, oestrogen receptor; NACT, neoadjuvant chemotherapy; NET, neoadjuvant endocrine therapy; RCT, randomised controlled trial; RR, risk ratio

[1] *95% confidence interval crosses both no effect (1) and minimally important difference (1.25) based on GRADE default values; <300 events*

[2] *14% of sample ER-*

[3] *95% confidence interval crosses both no effect (1) and minimally important difference (0.8) based on GRADE default values; <300 events*

[4] *95% confidence interval crosses both no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values; <300 events*

[5] *<300 events*

[6] *14% of Semiglazov 2007 sample ER-; this study has 77% of weight in the analysis*

[7] *Groups not comparable; more advanced T stage, N stage, and Grade in NACT arm. Also higher rates of PR- and adjuvant radiotherapy in NACT arm*

GRADE tables for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

Table 22: Clinical evidence profile: Comparison 1. Postmastectomy radiotherapy to the chest wall and regional nodes after neoadjuvant chemotherapy versus no radiotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute	Quality	Importance
Locoregional recurrence - mixed population (4 to 10 year follow-up)												
4	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	95/762 (12.5%)	55/246 (22.4%)	HR 0.38 (0.26 to 0.56)	132 fewer per 1000 (from 91 fewer to 160 fewer)	VERY LOW	CRITICAL
Locoregional recurrence - T stage subgroups - ct2 (5 to 10 year follow-up)												
3	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	5/108 (4.6%)	12/91 (13.2%)	HR 0.32 (0.12 to 0.84)	88 fewer per 1000 (from 20 fewer to 115 fewer)	VERY LOW	CRITICAL
Locoregional recurrence - T stage subgroups - ct3 (5 to 10 year follow-up)												
3	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	22/245 (9%)	20/75 (26.7%)	HR 0.19 (0.09 to 0.4)	209 fewer per 1000 (from 150 fewer to 239 fewer)	VERY LOW	CRITICAL
Locoregional recurrence - T stage subgroups - ct4 (5 to 10 year follow-up)												
3	Observational studies	Serious[1]	Serious[4]	No serious indirectness	Serious[2]	None	57/352 (16.2%)	20/56 (35.7%)	HR 0.35 (0.19 to 0.68)	214 fewer per 1000 (from 98 fewer to 277 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute		
Locoregional recurrence - T stage subgroups - pt0/Tis (7.7 to 10 year follow-up)												
2	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	5/79 (6.3%)	5/41 (12.2%)	HR 0.42 (0.12 to 1.55)	69 fewer per 1000 (from 106 fewer to 61 more)	VERY LOW	CRITICAL
Locoregional recurrence - T stage subgroups - pt2 (7.7 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[5]	Serious[2]	None	3/36 (8.3%)	6/39 (15.4%)	HR 0.33 (0.09 to 1.23)	100 fewer per 1000 (from 139 fewer to 32 more)	VERY LOW	CRITICAL
Locoregional recurrence - T stage subgroups - pt3 (7.7 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[5]	Serious[2]	None	2/11 (18.2%)	3/7 (42.9%)	HR 0.29 (0.05 to 1.77)	279 fewer per 1000 (from 401 fewer to 200 more)	VERY LOW	CRITICAL
Locoregional recurrence - T stage subgroups - pt4 (7.7 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[5]	Serious[2]	None	9/31 (29%)	1/6 (16.7%)	HR 1.8 (0.34 to 9.67)	113 more per 1000 (from 107 fewer to 662 more)	VERY LOW	CRITICAL
Locoregional recurrence - N stage subgroups - cn0 (5 to 10 year follow-up)												
3	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	12/128 (9.4%)	15/68 (22.1%)	HR 0.31 (0.14 to 0.69)	146 fewer per 1000 (from 63	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute		
										fewer to 186 fewer)		
Locoregional recurrence - N stage subgroups - cn1 (5 to 10 year follow-up)												
3	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	28/340 (8.2%)	21/127 (16.5%)	HR 0.41 (0.22 to 0.78)	94 fewer per 1000 (from 34 fewer to 126 fewer)	VERY LOW	CRITICAL
Locoregional recurrence - N stage subgroups - cn2 (5 to 7.7 year follow-up)												
2	Observational studies	Serious[1]	No serious inconsistency	Serious[6]	Serious[2]	None	12/54 (22.2%)	4/11 (36.4%)	HR 0.43 (0.12 to 1.57)	187 fewer per 1000 (from 311 fewer to 145 more)	VERY LOW	CRITICAL
Locoregional recurrence - N stage subgroups - cn2/3 (10 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	28/232 (12.1%)	11/27 (40.7%)	HR 0.13 (0.05 to 0.36)	342 fewer per 1000 (from 236 fewer to 382 fewer)	VERY LOW	CRITICAL
Locoregional recurrence - N stage subgroups - cn3 (5 year follow-up)												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	1/6 (16.7%)	1/1 (100%)	HR 0.12 (0 to 5.81)	0 fewer per 1000 (from -2147483648 fewer to 0 more)	VERY LOW	CRITICAL
Locoregional recurrence - N stage subgroups - pn0 (4.75 to 10 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute		
4	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	6/246 (2.4%)	17/148 (11.5%)	HR 0.28 (0.12 to 0.69)	81 fewer per 1000 (from 34 fewer to 100 fewer)	VERY LOW	CRITICAL
Locoregional recurrence - N stage subgroups - pn1 (7.7 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[5]	Serious[2]	None	6/34 (17.6%)	3/29 (10.3%)	HR 1.39 (0.38 to 5.15)	37 more per 1000 (from 63 fewer to 327 more)	VERY LOW	CRITICAL
Locoregional recurrence - N stage subgroups - pn2 (7.7 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[5]	Serious[2]	None	7/36 (19.4%)	5/16 (31.3%)	HR 0.42 (0.12 to 1.41)	167 fewer per 1000 (from 269 fewer to 98 more)	VERY LOW	CRITICAL
Locoregional recurrence - N stage subgroups - pn3 (7.7 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[5]	Serious[2]	None	1/22 (4.5%)	2/13 (15.4%)	HR 0.48 (0.05 to 5.02)	77 fewer per 1000 (from 146 fewer to 414 more)	VERY LOW	CRITICAL
Locoregional recurrence - T & N stage subgroups - ct3n0 (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	5/119 (4.2%)	10/43 (23.3%)	HR 0.15 (0.05 to 0.46)	194 fewer per 1000 (from 118 fewer to 219 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute		
DFS - Whole sample (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	10/118 (8.5%)	15/43 (34.9%)	HR 0.5 (0.21 to 1.21)	156 fewer per 1000 (from 263 fewer to 56 more)	VERY LOW	CRITICAL
DFS - pn0 (4.75 to 10 year follow-up)												
2	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	32/183 (17.5%)	19/102 (18.6%)	HR 1.15 (0.62 to 2.13)	25 more per 1000 (from 66 fewer to 169 more)	VERY LOW	CRITICAL
OS - mixed populations (4 to 10 year follow-up)												
4	Observational studies	Serious[1]	Serious[7]	No serious indirectness	No serious imprecision	None	417/762 (54.7%)	113/246 (45.9%)	HR 1.35 (1.1 to 1.66)	105 more per 1000 (from 32 more to 180 more)	VERY LOW	IMPORTANT
OS - T stage subgroups - ct1/2 (3.25 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[8]	No serious imprecision	None	559/3087 (18.1%)	238/1236 (19.3%)	HR 0.84 (0.72 to 0.98)	28 fewer per 1000 (from 3 fewer to 50 fewer)	VERY LOW	IMPORTANT
OS - T stage subgroups - ct2 (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	1/11 (9.1%)	3/11 (27.3%)	HR 0.4 (0.05 to 2.93)	153 fewer per 1000 (from 257 fewer to 334 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute		
OS - T stage subgroups - ct3 (3.25 to 5 year follow-up)												
2	Observational studies	Serious[1]	Serious[9]	Serious[8]	No serious imprecision	None	554/2366 (23.4%)	207/590 (35.1%)	HR 0.68 (0.57 to 0.8)	96 fewer per 1000 (from 59 fewer to 133 fewer)	VERY LOW	IMPORTANT
OS - T stage subgroups - ct4 (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	17/40 (42.5%)	6/7 (85.7%)	HR 0.31 (0.1 to 0.97)	404 fewer per 1000 (from 9 fewer to 680 fewer)	VERY LOW	IMPORTANT
OS - T stage subgroups - pt0/Tis (10 year follow-up)												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	Strong association[3]	14/62 (22.6%)	8/12 (66.7%)	HR 0.16 (0.05 to 0.5)	505 fewer per 1000 (from 244 fewer to 613 fewer)	LOW	IMPORTANT
OS - N stage subgroups - cn0 (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	1/9 (11.1%)	5/5 (100%)	HR 0.12 (0.02 to 0.63)	-	VERY LOW	IMPORTANT
OS - N stage subgroups - cn1 (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	15/37 (40.5%)	5/17 (29.4%)	HR 1.21 (0.47 to 3.1)	50 more per 1000 (from 143 fewer to 366 more)	VERY LOW	IMPORTANT
OS - N stage subgroups - cn2 (5 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute		
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	5/28 (17.9%)	3/4 (75%)	HR 0.18 (0.02 to 1.52)	529 fewer per 1000 (from 723 fewer to 128 more)	VERY LOW	IMPORTANT
OS - N stage subgroups - cn3 (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	4/6 (66.7%)	1/1 (100%)	HR 0.47 (0.04 to 5.79)	-	VERY LOW	IMPORTANT
OS - N stage subgroups - pn0 (4.75 to 10 year follow-up)												
3	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	25/183 (13.7%)	12/102 (11.8%)	HR 1.24 (0.97 to 1.6)	26 more per 1000 (from 3 fewer to 64 more)	VERY LOW	IMPORTANT
OS - N stage subgroups - pn1 (3.25 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[8]	No serious imprecision	None	493/3186 (15.5%)	243/1318 (18.4%)	HR 0.84 (0.71 to 0.98)	27 fewer per 1000 (from 3 fewer to 50 fewer)	VERY LOW	IMPORTANT
OS - N stage subgroups - pn2/3 (3.25 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	Serious[8]	No serious imprecision	None	611/2238 (27.3%)	197/501 (39.3%)	HR 0.68 (0.57 to 0.8)	105 fewer per 1000 (from 64 fewer to 145 fewer)	VERY LOW	IMPORTANT
OS - N stage subgroups - cn1pn0 (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	99/651 (15.2%)	97/530 (18.3%)	HR 0.83 (0.63 to 1.1)	29 fewer per 1000 (from 63	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute		
										fewer to 16 more)		
OS - N stage subgroups - cn2/3pn0 (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	40/252 (15.9%)	23/127 (18.1%)	HR 0.78 (0.47 to 1.32)	37 fewer per 1000 (from 91 fewer to 51 more)	VERY LOW	IMPORTANT
OS - T & N stage subgroups - ct1/2pn0 (3.25 to 5 year follow-up)												
2	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	96/1379 (7%)	116/1119 (10.4%)	HR 0.69 (0.53 to 0.91)	31 fewer per 1000 (from 9 fewer to 47 fewer)	VERY LOW	IMPORTANT
OS - T & N stage subgroups - ct3/4pn0 (3.25 to 5 year follow-up)												
2	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	195/1486 (13.1%)	113/616 (18.3%)	HR 0.73 (0.58 to 0.93)	46 fewer per 1000 (from 12 fewer to 73 fewer)	VERY LOW	IMPORTANT
OS - T & N stage subgroups - pt0/tisn0 (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	56/399 (14%)	36/277 (13%)	HR 1.03 (0.68 to 1.56)	4 more per 1000 (from 40 fewer to 65 more)	VERY LOW	IMPORTANT
OS - T & N stage subgroups - pt1/2N0 (5 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	83/504 (16.5%)	84/380 (22.1%)	HR 0.73 (0.53 to 0.99)	49 fewer per 1000 (from 2 fewer to 90 fewer)	VERY LOW	IMPORTANT

DFS, disease-free survival; HR, hazard ratio; OS, overall survival
[1] Significant differences in patient characteristics between arms for all trials
[2] <300 events
[3] HR and 95% CI<0.5

[4] Significant unexplained heterogeneity; I2 85%. Not possible to explore sources of heterogeneity as additional subgroups of interest identified by the committee were not reported
[5] Intervention: 84% received radiotherapy to chest wall and regional nodes; remainder just received radiotherapy to chest wall
[6] Intervention: 84% received radiotherapy to chest wall and regional nodes in the trial with the largest weight; remainder just received radiotherapy to chest wall
[7] Significant heterogeneity; I2 64%. Explored in subsequent subgroup analysis
[8] Intervention: unclear what percentage received radiotherapy to the regional nodes
[9] Significant unexplained heterogeneity; I2 76%. Not possible to explore sources of heterogeneity as additional subgroups of interest identified by the committee were not reported

GRADE tables for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

Table 23: Clinical evidence profile: Comparison 1. Platinum containing regimen vs non-platinum containing regimen in adults with triple negative invasive breast cancer

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum	Non platinum NAC	Relative (95% CI)	Absolute	Quality	Importance
Pathological complete response rate (assessed with: PCR at surgery)												
5[1,2,3,4,5]	Randomised trials	Serious[6]	No serious inconsistency[7]	Serious[8]	No serious imprecision	None	272/510 (53.3%)	188/497 (37.8%)	RR 1.41 (1.23 to 1.62)	155 more per 1000 (from 87 more to 235 more)	LOW	CRITICAL
Overall Survival - 5 year overall survival (follow-up median 55 months)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[9]	None	39/47 (83%)	31/44 (70.5%)	RR 1.18 (0.93 to 1.48)	127 more per 1000 (from 49 fewer to 338 more)	LOW	CRITICAL
Disease-free survival (follow-up median 55 months; assessed with: 5 year relapse free survival)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[9]	None	36/47 (76.6%)	25/44 (56.8%)	RR 1.35 (1 to 1.82)	199 more per 1000 (from 0 more to 466 more)	LOW	IMPORTANT
Overall response rate (assessed with: ORR after treatment)												
2[1,4]	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[8]	Very serious[9]	None	78/94 (83%)	67/90 (74.4%)	RR 1.11 (0.96 to 1.29)	82 more per 1000 (from 30 fewer to 216 more)	VERY LOW	IMPORTANT
Breast conservation rate												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum	Non platinum NAC	Relative (95% CI)	Absolute		
2[4,5]	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[8]	Serious[10]	None	160/268 (59.7%)	124/258 (48.1%)	RR 1.24 (1.06 to 1.46)	115 more per 1000 (from 29 more to 221 more)	LOW	IMPORTANT
Treatment related morbidity - Grade 3/4 Adverse events												
2[4,5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Very serious[9]	None	101/268 (37.7%)	79/258 (30.6%)	RR 1.23 (0.98 to 1.56)	70 more per 1000 (from 6 fewer to 171 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Anaemia												
2[4,5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Very serious[9]	None	14/268 (5.2%)	2/258 (0.78%)	RR 5.6 (1.48 to 21.16)	36 more per 1000 (from 4 more to 156 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Leucopenia												
2[4,5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Very serious[9]	None	44/268 (16.4%)	29/258 (11.2%)	RR 1.46 (0.94 to 2.26)	52 more per 1000 (from 7 fewer to 142 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Neutropenia												
3[1,4,5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Serious[12]	None	174/315 (55.2%)	96/302 (31.8%)	RR 1.73 (1.44 to 2.07)	232 more per 1000 (from 140 more to 340 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Thrombocytopenia												
3[1,4,5]	Randomised trials	No serious	No serious inconsistency	Very serious[11]	Serious[12]	None	66/315 (21%)	9/302 (3%)	RR 6.68 (3.46 to 12.92)	169 more per 1000 (from 73	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum	Non platinum NAC	Relative (95% CI)	Absolute		
		risk of bias								more to 355 more)		
Treatment related morbidity - Febrile neutropenia												
2[4,5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[8,11]	Serious[12]	None	41/268 (15.3%)	23/258 (8.9%)	RR 1.72 (1.06 to 2.78)	64 more per 1000 (from 5 more to 159 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Hypersensitivity												
14	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[9]	Very serious[8,9]	None	1/47 (2.1%)	2/46 (4.3%)	RR 0.49 (0.05 to 5.21)	22 fewer per 1000 (from 41 fewer to 183 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Fatigue												
2[4,5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Very serious[9]	None	35/268 (13.1%)	29/258 (11.2%)	RR 1.16 (0.73 to 1.85)	18 more per 1000 (from 30 fewer to 96 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Infection												
1[4]	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[9]	Very serious[9]	None	4/47 (8.5%)	4/46 (8.7%)	RR 0.98 (0.26 to 3.68)	2 fewer per 1000 (from 64 fewer to 233 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Diarrheoa												
1[5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Very serious[9]	None	5/221 (2.3%)	3/212 (1.4%)	RR 1.6 (0.39 to 6.61)	8 more per 1000 (from 9 fewer to 79 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Hypertension												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum	Non platinum NAC	Relative (95% CI)	Absolute	Quality	Importance
1[5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Very serious[9]	None	10/221 (4.5%)	14/212 (6.6%)	RR 0.69 (0.31 to 1.51)	20 fewer per 1000 (from 46 fewer to 34 more)	VERY LOW	IMPORTANT
Treatment related morbidity - ALT/AST elevation												
2[1,5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Very serious[9]	None	18/268 (6.7%)	17/256 (6.6%)	RR 1 (0.56 to 1.76)	0 fewer per 1000 (from 29 fewer to 50 more)	VERY LOW	IMPORTANT
Treatment related morbidity - Peripheral neuropathy												
2[1,5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Very serious[9]	None	30/268 (11.2%)	25/256 (9.8%)	RR 1.13 (0.72 to 1.78)	13 more per 1000 (from 27 fewer to 76 more)	VERY LOW	IMPORTANT
Treatment related morbidity - ST-T changes												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[8]	Very serious[9]	None	9/47 (19.1%)	11/44 (25%)	RR 0.77 (0.35 to 1.67)	58 fewer per 1000 (from 162 fewer to 167 more)	VERY LOW	IMPORTANT
Treatment related mortality												
1[5]	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[11]	Very serious[9]	None	1/221 (0.45%)	0/212 (0%)	RR 2.88 (0.12 to 70.27)	-	VERY LOW	IMPORTANT

CI: confidence interval; NAC: Neoadjuvant chemotherapy; ORR: Overall response rate; pCR: Pathological complete response; RR: risk ratio; TNBC: Triple Negative Breast Cancer

[1] Zhang 2016

[2] Ando 2014

[3] Von Minckwitz 2014

[4] Alba 2012

[5] Sikov 2014

[6] Downgraded by 1 level for serious risk of bias. TNBC is a subgroup in Ando 2014 and Von Minckwitz 2014 .Segregated information is not available regarding comparability of intervention and control groups at baseline

[7] *Serious inconsistency. I square =56%.*
[8] *Downgraded by 1 level for serious indirectness. Alba 2012 is restricted to patients with basal like breast cancer*
[9] *Downgraded by 2 levels for very serious imprecision;<300 events;95% CI crosses limits for no effect.*
[10] *Downgraded by 1 level for serious imprecision; 95% CI crosses limits for no effect*
[11] *Downgraded by 1 level for serious indirectness due to simultaneous treatment with bevacizumab*
[12] *Downgraded by 1 level for serious imprecision; < 300 events*

Appendix G – Economic evidence study selection

Economic evidence study selection for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

See Supplement 1: Health economics literature review for details of economic study selection.

Economic evidence study selection for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

See Supplement 1: Health economics literature review for details of economic study selection.

Economic evidence study selection for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

See Supplement 1: Health economics literature review for details of economic study selection.

Economic evidence study selection for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

See Supplement 1: Health economics literature review for details of economic study selection.

Appendix H – Economic evidence tables

Economic evidence tables for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

No economic evidence was identified for this review.

Economic evidence tables for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

No economic evidence was identified for this review.

Economic evidence tables for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

No economic evidence was identified for this review.

Economic evidence tables for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

No economic evidence was identified for this review.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

No economic evidence was identified for this review.

Health economic evidence profiles for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

No economic evidence was identified for this review.

Health economic evidence profiles for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

No economic evidence was identified for this review.

Health economic evidence profiles for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

No economic evidence was identified for this review.

Appendix J – Health economic analysis

Health economic analysis for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

No health economic analysis was conducted for this review.

Health economic analysis for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

No health economic analysis was conducted for this review.

Health economic analysis for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

No health economic analysis was conducted for this review.

Health economic analysis for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

No health economic analysis was conducted for this review.

Appendix K – Excluded studies

Excluded studies for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

Clinical studies

Excluded studies – Review question 10.1 What is the effectiveness of neoadjuvant chemotherapy?	
Study	**Reason for exclusion**
Andreopoulou, E., Vigoda, I. S., Valero, V., Hershman, D. L., Raptis, G., Vahdat, L. T., Han, H. S., Wright, J. J., Pellegrino, C. M., Cristofanilli, M., Alvarez, R. H., Fehn, K., Fineberg, S., Sparano, J. A., Phase I-II study of the farnesyl transferase inhibitor tipifarnib plus sequential weekly paclitaxel and doxorubicin-cyclophosphamide in HER2/neu-negative inflammatory carcinoma and non-inflammatory estrogen receptor-positive breast carcinoma, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 141, 429-35, 2013	Non comparative study
Aruga, T., Suzuki, E., Horiguchi, S., Sekine, S., Kitagawa, D., Saji, S., Funata, N., Toi, M., Kuroi, K., Correlation of number of tumor infiltrating FOXP3-positive cells after primary systemic chemotherapy with anti-tumor response in breast cancer patients, Journal of Clinical Oncology, 26, 22219, 2008	Conference abstract
Aseyev, O., Ribeiro, J. M., Cardoso, F., Review on the clinical use of eribulin mesylate for the treatment of breast cancer, Expert Opinion on Pharmacotherapy, 17, 589-600, 2016	Expert review - no relevant phase II trials included.
Bear, H. D., Anderson, S., Smith, R. E., Geyer, C. E., Jr., Mamounas, E. P., Fisher, B., Brown, A. M., Robidoux, A., Margolese, R., Kahlenberg, M. S., Paik, S., Soran, A., Wickerham, D. L., Wolmark, N., Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27, Journal of clinical oncology, 24, 2019-27, 2006	Compares addition of taxane to AC neoadjuvant chemotherapy
Bergh,J., Jonsson,P.E., Glimelius,B., Nygren,P., A systematic overview of chemotherapy effects in breast cancer, Acta Oncologica, 40, 253-281, 2001	Systematic review - outdated.
Berruti, A., Brizzi, M. P., Generali, D., Ardine, M., Dogliotti, L., Bruzzi, P., Bottini, A., Presurgical systemic treatment of nonmetastatic breast cancer: facts and open questions, Oncologist, 13, 1137-48, 2008	Expert review
Bonilla, L., Ben-Aharon, I., Vidal, L., Gafter-Gvili, A., Leibovici, L., Stemmer, S. M., Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials, Journal of the National Cancer Institute, 102, 1845-54, 2010	Systematic review - comparison not in PICO
Bozza, C., Osa, E. O., Puglisi, F., Primary therapy in breast cancer: What have we learned from landmark trials?, Women's Health, 9, 583-593, 2013	Expert review
Burris, H. A., 3rd, Docetaxel (Taxotere) in HER-2-positive patients and in combination with trastuzumab (Herceptin), Seminars in Oncology, 27, 19-23, 2000	Intervention not in review protocol

Excluded studies – Review question 10.1 What is the effectiveness of neoadjuvant chemotherapy?	
Study	**Reason for exclusion**
Chang, H. R., Trastuzumab-based neoadjuvant therapy in patients with HER2-positive breast cancer, Cancer, 116, 2856-2867, 2010	Intervention not in PICO - trials compare addition of Traztuzumab
Chang, J., Liu, J., Li, H., Li, J., Mu, Y., Feng, B., Expression of ERbeta gene in breast carcinoma and the relevance in neoadjuvant therapy, Oncology Letters, 13, 1641-1646, 2017	No relevant data/RCT referred to in abstract does not appear to have been published.
Chen, X. S., Yuan, Y., Garfield, D. H., Wu, J. Y., Huang, O., Shen, K. W., Both carboplatin and bevacizumab improve pathological complete remission rate in neoadjuvant treatment of triple negative breast cancer: A meta-analysis, PLoS ONE, 9 (9) (no pagination), 2014	No relevant RCTs
Chen, Y. Y., Wang, L. W., Chen, F. F., Wu, B. B., Xiong, B., Efficacy, safety and administration timing of trastuzumab in human epidermal growth factor receptor 2 positive breast cancer patients: A meta-analysis, Experimental and Therapeutic Medicine, 11, 1721-1733, 2016	No relevant RCTs
Chen, Z. L., Shen, Y. W., Li, S. T., Li, C. L., Zhang, L. X., Lv, M., Lin, Y. Y., Wang, X., Yang, J., The efficiency and safety of trastuzumab and lapatinib added to neoadjuvant chemotherapy in Her2-positive breast cancer patients: A randomized meta-analysis, OncoTargets and Therapy, 9, 3233-3247, 2016	No relevant RCTs
Clavarezza, M., Puntoni, M., Gennari, A., Paleari, L., Provinciali, N., D'Amico, M., DeCensi, A., Dual block with lapatinib and trastuzumab versus single-agent trastuzumab combined with chemotherapy as neoadjuvant treatment of HER2-positive breast cancer: A meta-analysis of randomized trials, Clinical Cancer ResearchClin Cancer Res, 22, 4594-4603, 2016	Systematic review - intervention not in PICO -chemotherapy the same in both arms (trials compare lapatinib trastuzumab vs trastuzumab).
Cleator, S. J., Makris, A., Ashley, S. E., Lal, R., Powles, T. J., Good clinical response of breast cancers to neoadjuvant chemoendocrine therapy is associated with improved overall survival, Annals of Oncology, 16, 267-72, 2005	Chemoendocrine study
Colleoni, M., Orvieto, E., Nole, F., Orlando, L., Minchella, I., Viale, G., Peruzzotti, G., Robertson, C., Noberasco, C., Galimberti, V., Sacchini, V., Veronesi, P., Zurrida, S., Orecchia, R., Goldhirsch, A., Prediction of response to primary chemotherapy for operable breast cancer, European journal of cancer, 35, 574-579, 1999	Non-randomised study
Dent, S., Oyan, B., Honig, A., Mano, M., Howell, S., HER2-targeted therapy in breast cancer: A systematic review of neoadjuvant trials, Cancer Treatment Reviews, 39, 622-631, 2013	Intervention not in PICO - compares addition of lapatinib or trastuzumab
Derleth, C., Mayer, I. A., Antiangiogenic therapies in early-stage breast cancer, Clinical Breast Cancer, 10 Suppl 1, E23-31, 2010	Expert review

Excluded studies – Review question 10.1 What is the effectiveness of neoadjuvant chemotherapy?	
Study	**Reason for exclusion**
D'Orazio, A. I., O'Shaughnessy, J., Seidman, A. D., Neoadjuvant docetaxel augments the efficacy of preoperative docetaxel/cyclophosphamide in operable breast cancer: First results of NSABP B-27, Clinical Breast Cancer, 2, 266-268, 2002	No relevant comparison
Doval, D. C., Dutta, K., Batra, U., Talwar, V., Neoadjuvant chemotherapy in breast cancer: review of literature, Journal of the Indian Medical Association, 111, 629-631, 2013	Expert review
Ferrario, C., Batist, G., Advances in the approach to novel drug clinical development for breast cancer, Expert Opinion on Drug Discovery, 9, 647-668, 2014	Expert review
Fisher, B., Brown, A., Mamounas, E., Wieand, S., Robidoux, A., Margolese, R. G., Cruz Jr, A. B., Fisher, E. R., Wickerham, D. L., Wolmark, N., DeCillis, A., Hoehn, J. L., Lees, A. W., Dimitrov, N. V., Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from national surgical adjuvant breast and bowel project B-18, Journal of Clinical Oncology, 15, 2483-2493, 1997	Published before 1998/more recent results published in Fisher 1998, Rastogi 2008, and Wolmark 2001.
Fisher, E. R., Wang, J., Bryant, J., Fisher, B., Mamounas, E., Wolmark, N., Pathobiology of preoperative chemotherapy: Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-18, Cancer, 95, 681-695, 2002	No relevant data
Gennari, A., Amadori, D., De Lena, M., Nanni, O., Bruzzi, P., Lorusso, V., Manzione, L., Conte, P. F., Lack of benefit of maintenance paclitaxel in first-line chemotherapy in metastatic breast cancer, Journal of Clinical Oncology, 24, 3912-3918, 2006	Metastatic population, compares paclitaxel maintenance versus no maintenance chemo
Giampaglia, M., Chiuri, V. E., Tinelli, A., De Laurentiis, M., Silvestris, N., Lorusso, V., Lapatinib in breast cancer: Clinical experiences and future perspectives, Cancer Treatment Reviews, 36, S72-S79, 2010	expert review - lapatinib trials
Gianni, L., Dafni, U., Gelber, R. D., Azambuja, E., Muehlbauer, S., Goldhirsch, A., Untch, M., Smith, I., Baselga, J., Jackisch, C., Cameron, D., Mano, M., Pedrini, J. L., Veronesi, A., Mendiola, C., Pluzanska, A., Semiglazov, V., Vrdoljak, E., Eckart, M. J., Shen, Z., Skiadopoulos, G., Procter, M., Pritchard, K. I., Piccart-Gebhart, M. J., Bell, R., Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: A 4-year follow-up of a randomised controlled trial, The Lancet Oncology, 12, 236-244, 2011	Intervention not in PICO - trastuzumab vs observation after neoadjuvant CT
Gianni, L., Pienkowski, T., Im, Y. H., Tseng, L. M., Liu, M. C., Lluch, A., Staroslawska, E., de la Haba-Rodriguez, J., Im, S. A., Pedrini, J. L., Poirier, B., Morandi, P., Semiglazov, V., Srimuninnimit, V., Bianchi, G. V., Magazzu, D., McNally, V., Douthwaite, H., Ross, G., Valagussa, P., 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial, The Lancet Oncology, 17, 791-800, 2016	Not neoadjuvant anthracyline regimen
Hortobagyi, G. N., Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes: Von Minckwitz G, Untch M, Blohmer J-U, et al (German Breast Group, Neu-Isenburg, Germany; Helios-Klinikum, Berlin, Germany; St Gertrauden Krankenhaus, Berlin, Germany; Et al) J Clin Oncol 30:1796-1804, 2012, Breast Diseases, 23, 374-375, 2012	Commentary article

Excluded studies – Review question 10.1 What is the effectiveness of neoadjuvant chemotherapy?	
Study	**Reason for exclusion**
Islam, M. S., Islam, M. S., Parvin, S., Ahmed, M. U., Bin Sayeed, M. S., Uddin, M. M., Hussain, S. M., Hasnat, A., Effect of GSTP1 and ABCC4 gene polymorphisms on response and toxicity of cyclophosphamide-epirubicin-5-fluorouracil-based chemotherapy in Bangladeshi breast cancer patients, Tumour BiologyTumour Biol, 36, 5451-7, 2015	Not a randomised trial
Janakiram, M., Zhang, L., White, R., Ayyappan, S., Sparano, J., Tumor infiltrating lymphocytes (TILs) in breast cancer: A meta-analysis of response to neoadjuvant chemotherapy based on TIL status, Cancer Research. Conference: 36th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 73, 2013	Intervention not in PICO - Conference abstract about predictive factor for tumour response
Jeong, J. H., Jung, S. Y., Park, I. H., Lee, K. S., Kang, H. S., Kim, S. W., Kwon, Y., Kim, E. A., Ko, K. L., Nam, B. H., Lee, S., Ro, J., Predictive factors of pathologic complete response and clinical tumor progression after preoperative chemotherapy in patients with stage II and III breast cancer, Investigational New Drugs, 30, 408-16, 2012	Intervention not in PICO - compares different types of neoadjuvant chemotherapy
Khasraw, M., Bell, R., Primary systemic therapy in HER2-amplified breast cancer: A clinical review, Expert Review of Anticancer TherapyExpert Rev Anticancer Ther, 12, 1005-1013, 2012	Expert review - primary trastuzumab
Knoop, A. S., Knudsen, H., Balslev, E., Rasmussen, B. B., Overgaard, J., Nielsen, K. V., Schonau, A., Gunnarsdottir, K., Olsen, K. E., Mouridsen, H., Ejlertsen, B., retrospective analysis of topoisomerase IIa amplifications and deletions as predictive markers in primary breast cancer patients randomly assigned to cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide, epirubicin, and fluorouracil: Danish Breast Cancer Cooperative Group, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 23, 7483-7490, 2005	Adjuvant chemotherapy trial
Kumar, P., Aggarwal, R., An overview of triple-negative breast cancer, Archives of Gynecology and Obstetrics, 293, 247-269, 2016	Expert review
Kumler, I., Christiansen, O. G., Nielsen, D. L., A systematic review of bevacizumab efficacy in breast cancer, Cancer Treatment Reviews, 40, 960-973, 2014	Systematic review - comparison not in PICO (/- bevacizumab)
Kuroi, K., Toi, M., Ohno, S., Nakamura, S., Iwata, H., Masuda, N., Sato, N., Tsuda, H., Kurosumi, M., Akiyama, F., Prognostic significance of subtype and pathologic response in operable breast cancer; a pooled analysis of prospective neoadjuvant studies of JBCRG, Breast Cancer, 22, 486-95, 2015	No relevant articles
Liedtke, C., Rody, A., New treatment strategies for patients with triple-negative breast cancer, Current Opinion in Obstetrics & GynecologyCurr Opin Obstet Gynecol, 27, 77-84, 2015	Expert review
Liedtke, C., Rody, A., Neoadjuvant therapy for patients with triple negative breast cancer (TNBC), Reviews on Recent Clinical Trials, 12, 73-80, 2017	expert review
Loibl, S., Jackisch, C., Lederer, B., Untch, M., Paepke, S., Kummel, S., Schneeweiss, A., Huober, J., Hilfrich, J., Hanusch, C., Gerber, B., Eidtmann, H., Denkert, C., Costa, S. D., Blohmer, J. U., Nekljudova, V., Mehta, K., von Minckwitz, G., Outcome after	No relevant articles

Excluded studies – Review question 10.1 What is the effectiveness of neoadjuvant chemotherapy?	
Study	**Reason for exclusion**
neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials, Breast Cancer Research and Treatment, 152, 377-387, 2015	
Ma, X., Wang, X., Huang, J., Chen, Y., Zhang, J., Zhang, B., Shi, C., Liu, L. L., Bevacizumab addition in neoadjuvant treatment increases the pathological complete response rates in patients with HER-2 negative breast cancer especially triple negative breast cancer: A meta-analysis, Plos One, 11 (8) (no pagination), 2016	Intervention not in PICO (/- bevacizumab)
Madarnas, Y., Trudeau, M., Franek, J. A., McCready, D., Pritchard, K. I., Messersmith, H., Adjuvant/neoadjuvant trastuzumab therapy in women with HER-2/neu-overexpressing breast cancer: A systematic review, Cancer treatment reviews, 34, 539-557, 2008	Comparison not in PICO (/- trastuzumab)
Makris,A., Powles,T.J., Ashley,S.E., Chang,J., Hickish,T., Tidy,V.A., Nash,A.G., Ford,H.T., A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer, Annals of Oncology, 9, 1179-1184, 1998	Chemendocrine study
Mathew, J., Asgeirsson, K. S., Cheung, K. L., Chan, S., Dahda, A., Robertson, J. F. R., Neoadjuvant chemotherapy for locally advanced breast cancer: A review of the literature and future directions, European Journal of Surgical Oncology, 35, 113-122, 2009	Expert review
Mauri, D., Pavlidis, N., Ioannidis, J. P. A., Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis, Journal of the National Cancer Institute, 97, 188-194, 2005	All relevant articles included in Mieog 2007 Cochrane review
Miller, K., Cortes, J., Hurvitz, S. A., Krop, I. E., Tripathy, D., Verma, S., Riahi, K., Reynolds, J. G., Wickham, T. J., Molnar, I., Yardley, D. A., HERMIONE: a randomized Phase 2 trial of MM-302 plus trastuzumab versus chemotherapy of physician's choice plus trastuzumab in patients with previously treated, anthracycline-naive, HER2-positive, locally advanced/metastatic breast cancer, BMC Cancer, 16, 352, 2016	No anthracylcines
Miller, Kd, McCaskill, Stevens W, Sisk, J, Loesch, Dm, Sledge, Gw, Randomized pilot trial of Taxotere (T) and doxorubicin (D) as primary chemotherapy for breast cancer, Proceedings of the American Society of Clinical Oncology, 18, 72a, Abstract 270, 1999	Abstract only
Nowak, A. K., Wilcken, N. R. C., Stockler, M. R., Hamilton, A., Ghersi, D., Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer, Lancet Oncology, 5, 372-380, 2004	Comparison not in PICO (taxane vs non-taxane regimens)
Pinto, A. C., Ades, F., de Azambuja, E., Piccart-Gebhart, M., Trastuzumab for patients with HER2 positive breast cancer: Delivery, duration and combination therapies, Breast, 22, S152-S155, 2013	Expert review
Pronzato, P., Cortesi, E., van der Rijt, C. C., Bols, A., Moreno-Nogueira, J. A., de Oliveira, C. F., Barrett-Lee, P., Ostler, P. J., Rosso, R., Epoetin alfa improves anemia and anemia-related, patient-reported outcomes in patients with breast cancer receiving myelotoxic chemotherapy: Results of a european, multicenter, randomized, controlled trial, Oncologist, 15, 935-943, 2010	Comparison not in PICO (Epoetin alfa vs BSC)
Puglisi, F., de Azambuja, E., de Castro, G., Jr., Demonty, G., Shrinking the tumor, shrinking the patient sample size: the early disclosure dilemma.[Erratum appears in J Clin Oncol. 2005 Dec 20;23(36):9445], Journal of Clinical Oncology, 23, 6803-4; author reply 6804-5, 2005	Letter

Excluded studies – Review question 10.1 What is the effectiveness of neoadjuvant chemotherapy?	
Study	**Reason for exclusion**
Rapoport, B. L., Demetriou, G. S., Moodley, S. D., Benn, C. A., When and how do i use neoadjuvant chemotherapy for breast cancer?, Current Treatment Options in Oncology, 15, 86-98, 2014	Expert review
Rapoport, B. L., Nayler, S., Demetriou, G. S., Moodley, S. D., Benn, C. A., Triple negative breast cancer pathological diagnosis and current chemotherapy treatment options, European Oncology and Haematology, 10, 35-42, 2014	Expert review
Rauschecker, Helmut Hf, Clarke, Mike J, Gatzemeier, Wolfgang, Recht, Abram, Systemic therapy for treating locoregional recurrence in women with breast cancer, Cochrane Database of Systematic Reviews, 2001	Comparison not in PICO (RT /- adjuvant chemo for recurrent disease)
Raut, N. V., Chordiya, N., NEO adjuvant chemotherapy in breast cancer: What have we learned so far?, Indian Journal of Medical and Paediatric Oncology, 31, 8-17, 2010	Expert review
Redden, M. H., Fuhrman, G. M., Neoadjuvant Chemotherapy in the Treatment of Breast Cancer, Surgical Clinics of North America, 93, 493-499, 2013	Expert review
Reinisch, M., Huober, J., von Minckwitz, G., Blohmer, J. U., Denkert, C., Hanusch, C., Jackisch, C., Kummel, S., Schneeweiss, A., Rhiem, K., Lederer, B., Untch, M., Nekljudova, V. V., Loibl, S., pCR rates in patients with bilateral breast cancer after neoadjuvant anthracycline-taxane based-chemotherapy - A retrospective pooled analysis of individual patients data of four German neoadjuvant trials, Breast, 32, 73-78, 2017	Comparisons not in PICO - describes 3 RCTs comparing different neoadjuvant chemotherapy regimens
Rocca, A., Schirone, A., Maltoni, R., Bravaccini, S., Cecconetto, L., Farolfi, A., Bronte, G., Andreis, D., Progress with palbociclib in breast cancer: Latest evidence and clinical considerations, Therapeutic Advances in Medical Oncology, 9, 83-105, 2017	Expert review
Sadeghi, S., Olevsky, O., Hurvitz, S. A., Profiling and targeting HER2-positive breast cancer using trastuzumab emtansine, Pharmacogenomics and Personalized Medicine, 7, 329-338, 2014	Expert review
Salgado, R., Denkert, C., Campbell, C., Savas, P., Nuciforo, P., Nucifero, P., Aura, C., de Azambuja, E., Eidtmann, H., Ellis, C. E., Baselga, J., Piccart-Gebhart, M. J., Michiels, S., Bradbury, I., Sotiriou, C., Loi, S., Tumor-Infiltrating Lymphocytes and Associations With Pathological Complete Response and Event-Free Survival in HER2-Positive Early-Stage Breast Cancer Treated With Lapatinib and Trastuzumab: A Secondary Analysis of the NeoALTTO Trial, JAMA oncology, 1, 448-454, 2015	Comparison not in PICO trastuzumab /- lapatinib
Seidenfeld, J., Samsom, D. J., Rothenberg, B. M., Bonnell, C. J., Ziegler, K. M., Aronson, N., HER2 testing to manage patients with breast cancer or other solid tumors, Evidence report/technology assessment, 1-362, 2008	Intervention not in PICO (HER2 testing)
Sendur, M. A. N., Aksoy, S., Altundag, K., Pertuzumab in HER2-positive breast cancer, Current medical research and opinion, 28, 1709-1716, 2012	Expert review
Simmons, C. E., Hogeveen, S., Leonard, R., Rajmohan, Y., Han, D., Wong, A., Lee, J., Brackstone, M., Boileau, J. F., Dinniwell, R., Gandhi, S., A Canadian national expert consensus on neoadjuvant therapy for breast cancer: Linking practice to evidence and beyond, Current Oncology, 22, S43-S53, 2015	No additional relevant RCTs

Excluded studies – Review question 10.1 What is the effectiveness of neoadjuvant chemotherapy?	
Study	**Reason for exclusion**
Smith, Ic, Primary chemotherapy in breast cancer: significantly enhanced clinical and pathological response with docetaxel, European Journal of Cancer, 35, S230, 1999	Comparison not in PICO (neoadjuvant docetaxel vs athracycline)
Sousa, B., Cardoso, F., Neoadjuvant treatment for HER-2-positive and triple-negative breast cancers, Annals of Oncology, 23, x237-x242, 2012	Expert review
Teshome, M., Hunt, K. K., Neoadjuvant therapy in the treatment of breast cancer, Surgical Oncology Clinics of North America, 23, 505-523, 2014	Expert review
Tian, M., Zhong, Y., Zhou, F., Xie, C., Zhou, Y., Liao, Z., Effect of neoadjuvant chemotherapy in patients with triple-negative breast cancer: A meta-analysis, Oncology LettersOncol, 9, 2825-2832, 2015	No relevant RCTs
Valachis, A., Mauri, D., Polyzos, N. P., Chlouverakis, G., Mavroudis, D., Georgoulias, V., Trastuzumab combined to neoadjuvant chemotherapy in patients with HER2-positive breast cancer: A systematic review and meta-analysis, Breast, 20, 485-490, 2011	Systematic review - comparison not in PICO (neoadjuvant chemo /- trastuzumab)
Valachis, A., Nearchou, A., Lind, P., Mauri, D., Lapatinib, trastuzumab or the combination added to preoperative chemotherapy for breast cancer: A meta-analysis of randomized evidence, Breast Cancer Research and Treatment, 135, 655-662, 2012	Systematic review-comparison not in PICO (neoadjuvant chemo plus trastuzumab or lapatinib)
Vrdoljak, E., Boban, M., Ban, M., Lapatinib in the treatment of HER-2 overexpressing breast cancer, Journal of B.U.ON., 16, 393-399, 2011	Intervention not in review protocol
Willems, A., Gauger, K., Henrichs, C., Harbeck, N., Antibody therapy for breast cancer, Anticancer Research, 25, 1483-9, 2005	Expert review
Wilson, S., Chia, S., New agents in locally advanced breast cancer, Current Opinion in Supportive & Palliative CareCurr, 8, 64-9, 2014	Expert review
Yaal-Hahoshen, N., Safra, T., Herceptin (trastuzumab): Adjuvant and neoadjuvant trials, Israel Medical Association Journal, 8, 416-421, 2006	No relevant RCTs
Yang, S. X., Polley, E., Lipkowitz, S., New insights on PI3K/AKT pathway alterations and clinical outcomes in breast cancer, Cancer Treatment ReviewsCancer Treat Rev, 45, 87-96, 2016	Expert review
Yuyama, Y., Yagihashi, A., Hirata, K., Ohmura, T., Suzuki, Y., Okamoto, J., Yamada, T., Okazaki, Y., Watanabe, Y., Okazaki, A., Toda, K., Okazaki, M., Yajima, T., Kameshima, H., Araya, J., Watanabe, N., Neoadjuvant intra-arterial infusion chemotherapy combined with hormonal therapy for locally advanced breast cancer, Oncology Reports, 7, 797-801, 2000	Not randomised trial

AC, doxorubicin, cyclophosphamide; CT, chemotherapy; PICO, population, intervention, comparison, outcome; RCT, randomised controlled trials; RT, radiotherapy

Economic studies

See Supplement 1: Health economics literature review for the list of excluded economic studies.

Excluded studies for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

Clinical studies

Excluded studies - RQ10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Bates, T., Riley, D. L., Houghton, J., Fallowfield, L., Baum, M., Breast cancer in elderly women: A Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone, British Journal of Surgery, 78, 591-594, 1991	ER status not assessed
Boccardo, F, Rubagotti, A, Amoroso, D, Sismondi, P, Sanctis, C, Farris, A, Scotto, T, Schieppati, G, Villa, E, Aldrighetti, D, Mesiti, M, Delia, P, Banducci, S, Mustacchi, G, Chemotherapy vs tamoxifen vs chemotherapy plus tamoxigen in patients with surgical mammary carcinoma with positive axillary lymph nodes and estradiol receptors. Eight years of evaluation, Tumori, 79 suppl, 10, 1993	Conference abstract
Cannon, Pm, Low, Scda, Ellis, Io, Elston, Cw, Blamey, Rw, Surgery versus tamoxifen in selected elderly patients with operable breast cancer: early results of a randomized trial, Breast Cancer Research and Treatment, 23, 182-182, 1992	Abstract only
Chakrabarti, J., Kenny, F. S., Syed, B. M., Robertson, J. F. R., Blamey, R. W., Cheung, K. L., A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-Final results at 20-year follow-up, Critical Reviews in Oncology/Hematology, 78, 260-264, 2011	ER status not assessed
Charehbili, A., Fontein, D. B. Y., Kroep, J. R., Liefers, G. J., Mieog, J. S. D., Nortier, J. W. R., Van de Velde, C. J. H., Neoadjuvant hormonal therapy for endocrine sensitive breast cancer: A systematic review, Cancer Treatment Reviews, 40, 86-92, 2014	Contains comparisons outside scope
Chia, Y. H., Ma, C. X., Ellis, M. J., Neoadjuvant Endocrine Therapy for Breast Cancer, Breast Diseases, 20, 355-357, 2009	Narrative review
De La Garza, J. G., Bargallo, E., Solorio, C., Ramirez, T., Salazar, F., Sanchez, J., Multicentric study with neoadjuvant endocrine therapy for breast conserving surgery. Experience in Mexico, 69, 2009	Conference abstract
Fallowfield, L., Quality of life in the elderly woman with breast cancer treated with tamoxifen and surgery or tamoxifen alone, Journal of Women's Health, 3, 17-20, 1994	ER status not assessed
Fentiman, I. S., Christiaens, M. R., Paridaens, R., Van Geel, A., Rutgers, E., Berner, J., De Keizer, G., Wildiers, J., Nagadowska, M., Legrand, C., Therasse, P., Treatment of operable breast cancer in the elderly: A randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy, European Journal of Cancer, 39, 309-316, 2003	ER status unknown for >50% of patients
Gazet -Ch, J., Markopoulos, C., Ford, H. T., Coombes, R. C., Bland, J. M., Dixon, R. C., Prospective randomised trial of tamoxifen versus surgery in elderly patients with breast cancer, Lancet, 1, 679-681, 1988	Insufficient presentation of results

Excluded studies - RQ10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Gazet, J. C., Ford, H. T., Coombes, R. C., Bland, J. M., Sutcliffe, R., Quilliam, J., Lowndes, S., Prospective randomized trial of tamoxifen vs surgery in elderly patients with breast cancer, European Journal of Surgical Oncology, 20, 207-214, 1994	Non-RCT - insufficient presentation of survival results
Gazet, J. C., Sutcliffe, R., A randomised trial comparing tamoxifen vs. surgery in patients over the age of 70 with operable breast cancer - Final results after 28 years of follow-up, European Journal of Surgical Oncology, 37, 754-757, 2011	Insufficient presentation of results
Goss, P. E., Strasser, K., Aromatase inhibitors in the treatment and prevention of breast cancer, Journal of Clinical Oncology, 19, 881-894, 2001	Non-systematic review
Guarneri, V., Frassoldati, A., Giovannelli, S., Borghi, F., Conte, P., Primary systemic therapy for operable breast cancer: A review of clinical trials and perspectives, Cancer Letters, 248, 175-185, 2007	Narrative review
Huang, L., Xu, A. M., Short-term outcomes of neoadjuvant hormonal therapy versus neoadjuvant chemotherapy in breast cancer: systematic review and meta-analysis of randomized controlled trials, Expert Review of Anticancer Therapy, 17, 327-334, 2017	Includes endocrine therapy not of interest (formestane, goserelin)
Johnston, S. J., Kenny, F. S., Syed, B. M., Robertson, J. F. R., Pinder, S. E., Winterbottom, L., Ellis, I. O., Blamey, R. W., Cheung, K. L., A randomised trial of primary tamoxifen versus mastectomy plus adjuvant tamoxifen in fit elderly women with invasive breast carcinoma of high oestrogen receptor content: Long-term results at 20 years of follow-up, Annals of Oncology, 23, 2296-2300, 2012	Insufficient presentation of results
Kenny, F. S., Robertson, J. F. R., Ellis, I. O., Elston, C. W., Blamey, R. W., Long-term follow-up of elderly patients randomized to primary tamoxifen or wedge mastectomy as initial therapy for operable breast cancer, Breast, 7, 335-339, 1998	ER status not assessed
Kenny, Fs, Ellis, Io, Elston, Cw, Robertson, Jfr, Blamey, Rw, Long term follow-up of elderly patients randomized to primary tamoxifen or wedge mastectomy as initial therapy for operable breast cancer, Breast (Edinburgh, Scotland), 6, 244, 1997	ER status not assessed
Leal, F., Liutti, V. T., Antunes dos Santos, V. C., Novis de Figueiredo, M. A., Macedo, L. T., Rinck Junior, J. A., Sasse, A. D., Neoadjuvant endocrine therapy for resectable breast cancer: A systematic review and meta-analysis, Breast, 24, 406-12, 2015	Contains comparisons outside scope
Lohrisch, C., Neoadjuvant hormonal therapy with anastrozole, Breast Cancer Research, 2 (1) (no pagination), 2000	Comparison outside scope - comparing different doses
London, S., Chemo edges out hormonal therapy at neoadjuvant stage, Oncology Report, 7, 2010	Commentary
London, S., Neoadjuvant AI therapy is effective in shrinking tumors, Oncology Report, 6, 2010	Commentary
Mansi, J. L., Smith, I. E., Walsh, G., A'Hern, R. P., Harmer, C. L., Sinnett, H. D., Trott, P. A., Fisher, C., McKinna, J. A., Primary medical therapy for operable breast cancer, European Journal of Cancer and Clinical Oncology, 25, 1623-1627, 1989	Non RCT - insufficient presentation of survival outcomes

Excluded studies - RQ10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Mauriac, L., Debled, M., Durand, M., Floquet, A., Boulanger, V., Dagada, C., Trufflandier, N., MacGrogan, G., Neoadjuvant tamoxifen for hormone-sensitive non-metastatic breast carcinomas in early postmenopausal women, Annals of Oncology, 13, 293-298, 2002	No comparison arm
Morgan, J. L., Reed, M. W., Wyld, L., Primary endocrine therapy as a treatment for older women with operable breast cancer - A comparison of randomised controlled trial and cohort study findings, European Journal of Surgical Oncology, 40, 676-684, 2014	Includes comparisons outside scope
Morgan, Jenna, Wyld, Lynda, Collins, Karen A, Reed, Malcolm W, Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus), Cochrane Database of Systematic Reviews, 2014	Contains comparisons outside scope
Novartis, Pharmaceuticals C, RAD001 and letrozole (femara) as preoperative therapy of primary breast cancer in post-menopausal women, Physician Data Query (PDQ), 2005	Protocol
Osterweil, N., Neoadjuvant anastrazole, other AIs lower mastectomy rate, Oncology Report, 12+13, 2012	Commentary
Robertson, J. F. R., Ellis, I. O., Elston, C. W., Blamey, R. W., Mastectomy or tamoxifen as initial therapy for operable breast cancer in elderly patients: 5-year follow-up, European Journal of Cancer Part A: General Topics, 28, 908-910, 1992	ER status not assessed
Robertson, J. F. R., Todd, J. H., Ellis, I. O., Elston, C. W., Blamey, R. W., Comparison of mastectomy with tamoxifen for treating elderly patients with operable breast cancer, British Medical Journal, 297, 511-514, 1988	ER status not assessed
Robertson, Jfr, Ellis, Io, Nicholson, Ri, Elston, Cw, Blamey, Rw, Late results of a randomized crossover study of mastectomy or tamoxifen in elderly patients with operable breast cancer, Breast Cancer Research and Treatment, 16, 176-176, 1990	Conference abstract
Robertson, Jfr, Todd, Jm, Ellis, Io, Nicholson, Ri, Elston, Cw, Blamey, Rw, Mastectomy or tamoxifen? A randomized crossover study in elderly patients with operable breast cancer, Breast Cancer Research and Treatment, 12, 111-111, 1988	Abstract only
Rose, C., Endocrine treatment of primary and advanced breast cancer, The International journal of biological markers, 3, 55-56, 1988	Narrative review
Semiglazov, V., Hormonal versus chemotherapy & neoadjuvant treatment, European Journal of Surgical Oncology, 36, 819-820, 2010	Conference abstract
Smith, I. E., Chua, S., Medical treatment of early breast cancer. IV: Neoadjuvant treatment, British Medical Journal, 332, 223-224, 2006	Narrative review
Spring, L. M., Gupta, A., Reynolds, K. L., Gadd, M. A., Ellisen, L. W., Isakoff, S. J., Moy, B., Bardia, A., Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis, JAMA oncology, 2, 1477-1486, 2016	Contains comparisons outside scope
Sugiu, K., Iwamoto, T., Kelly, C. M., Watanabe, N., Motoki, T., Ito, M., Ohtani, S., Higaki, K., Imada, T., Yuasa, T., Omori, M., Sonobe, H., Fujiwara, T., Matsuoka, J., Neoadjuvant Chemotherapy with or without Concurrent Hormone	Both arms include neoadjuvant chemotherapy

Excluded studies - RQ10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Therapy in Estrogen Receptor-Positive Breast Cancer: NACED-Randomized Multicenter Phase II Trial, Acta medica Okayama, 69, 291-9, 2015	
Takeda, K., Kanao, S., Okada, T., Ueno, T., Toi, M., Ishiguro, H., Mikami, Y., Tanaka, S., Togashi, K., MRI evaluation of residual tumor size after neoadjuvant endocrine therapy vs. neoadjuvant chemotherapy, European Journal of Radiology, 81, 2148-2153, 2012	Non-RCT - no survival outcomes
Thomas, J. S. J., Julian, H. S., Green, R. V., Cameron, D. A., Dixon, M. J., Histopathology of breast carcinoma following neoadjuvant systemic therapy: A common association between letrozole therapy and central scarring, Histopathology, 51, 219-226, 2007	Non-RCT - no survival outcomes
Thomas, R, Capasso, I, Matteis, A, Labonia, V, Landi, G, Nuzzo, F, Rossi, E, Montedoro, D, D'Aiuto, M, D'Aiuto, Gt, Melucci, M, Long term survival in elderly breast cancer patientstreated with tamoxifen (TAM) alone vs surgery followed by TAM, European Journal of Cancer, 34 suppl, S126, 1998	Conference abstract
Traa, M. J., Meijs, C. M. E. M., de Jongh, M. A. C., van der Borst, E. C. H. M., Roukema, J. A., Elderly women with breast cancer often die due to other causes regardless of primary endocrine therapy or primary surgical therapy, Breast, 20, 365-369, 2011	Non-RCT - Insufficient presentation of survival outcomes
Walker, G. A., Xenophontos, M., Chen, L. C., Cheung, K. L., Long-term efficacy and safety of exemestane in the treatment of breast cancer, Patient Preference and Adherence, 7, 245-258, 2013	Comparisons/populations outside scope
Wang, W., Liu, C., Zhou, W., Xia, T., Xie, H., Wang, S., Network Meta-Analysis of the Effectiveness of Neoadjuvant Endocrine Therapy for Postmenopausal, HR-Positive Breast Cancer, Scientific Reports, 6, 25615, 2016	Contains comparisons outside scope
Willsher, P. C., Robertson, J. F. R., Armitage, N. C., Morgan, D. A. L., Nicholson, R. I., Blamey, R. W., Locally advanced breast cancer: Long-term results of a randomized trial comparing primary treatment with tamoxifen or radiotherapy in post-menopausal women, European Journal of Surgical Oncology, 22, 34-37, 1996	Insufficient presentation of results
Willsher, P. C., Robertson, J. F. R., Jackson, L., Al-Hilaly, M., Blarney, R. W., Investigation of primary tamoxifen therapy for elderly patients with operable breast cancer, Breast, 6, 150-154, 1997	Insufficient presentation of results

ER, oestrogen receptor; RCT, randomised controlled trial

Economic studies

See Supplement 1: Health economics literature review for the list of excluded economic studies.

Excluded studies for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

Clinical studies

Excluded studies - RQ10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?	
Study	**Reason for Exclusion**
Bazan, J. G., White, J. R., The Role of Postmastectomy Radiation Therapy in Patients With Breast Cancer Responding to Neoadjuvant Chemotherapy, Seminars in radiation oncology, 26, 51-58, 2016	Non-systematic review
Bernier, J., Postmastectomy radiotherapy after neoadjuvant chemotherapy in breast cancer patients: A review, Critical Reviews in Oncology/Hematology, 93, 180-189, 2015	Non-systematic review
Fowble, B. L., Einck, J. P., Kim, D. N., McCloskey, S., Mayadev, J., Yashar, C., Chen, S. L., Hwang, E. S., Role of postmastectomy radiation after neoadjuvant chemotherapy in stage II-III breast cancer, International Journal of Radiation Oncology Biology Physics, 83, 494-503, 2012	Includes studies inconsistent with protocol
Gillon, P., Touati, N., Breton-Callu, C., Slaets, L., Cameron, D., Bonnefoi, H., Factors predictive of locoregional recurrence following neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancer: An analysis of the EORTC 10994/BIG 1-00 study, European Journal of Cancer, 79, 226-234, 2017	No data for comparison of interest
Kishan, A. U., McCloskey, S. A., Postmastectomy radiation therapy after neoadjuvant chemotherapy: Review and interpretation of available data, Therapeutic Advances in Medical Oncology, 8, 85-97, 2016	Non-systematic review
Mak, K. S., Harris, J. R., Radiotherapy Issues After Neoadjuvant Chemotherapy, Journal of the National Cancer Institute. Monographs, 2015, 87-9, 2015	Non-systematic review

Economic studies

See Supplement 1: Health economics literature review for the list of excluded economic studies.

Excluded studies for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

Clinical studies

Excluded studies - RQ10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neo-adjuvant chemotherapy?	
Study	**Reason for exclusion**
Amadori, D, Carrasco, E, Roesel, S, Labianca, R, Uziely, B, Soldatenkova, V, Moreau, V, Desaiah, D, Bauknecht, T, Martin, M, A randomized phase II non-comparative study of pemetrexed-carboplatin and gemcitabine-vinorelbine in anthracycline- and taxane-pretreated advanced breast cancer patients, International Journal of Oncology, 42, 1778-85, 2013	Exclusion for population: Advanced breast cancer cases
Chen, X. S., Yuan, Y., Garfield, D. H., Wu, J. Y., Huang, O., Shen, K. W., Both carboplatin and bevacizumab improve pathological complete remission rate in neoadjuvant treatment of triple negative breast cancer: A meta-analysis, PLoS ONE, 9 (9) (no pagination), 2014	Systematic review with no additional randomized controlled trials
Fan, Y, Xu, Bh, Yuan, P, Wang, Jy, Ma, F, Ding, Xy, Zhang, P, Li, Q, Cai, Rg, Results of a randomized phase II study demonstrate benefit of platinum-based regimen in the first-line treatment of triple negative breast cancer (TNBC), Cancer Research, 71, 2011	Exclusion by population: Metastasis and relapse cases
Gelmon, K., Dent, R., Mackey, J. R., Laing, K., McLeod, D., Verma, S., Targeting triple-negative breast cancer: Optimising therapeutic outcomes, Annals of Oncology, 23, 2223-2234, 2012	This review does not have any additional RCT for Cisplatin use in EBC
Gluz, O, Nitz, U, Christgen, M, Grischke, E-M, Forstbauer, H, Braun, Mw, Warm, M, Uleer, C, Aktas, B, Schumacher, C, Hackmann, J, Bangemann, N, Staib, P, Lindner, C, Kummel, S, Liedtke, C, Kates, Re, Wuerstlein, R, Kreipe, Hh, Harbeck, N, Efficacy of 12 weeks neoadjuvant nab-paclitaxel combined with carboplatinum vs. gemcitabine in triple-negative breast cancer: WSG-ADAPT TN randomized phase II trial, Journal of Clinical Oncology, 33, 2015	Exclusion by publication type : Meeting abstract
Golshan, M., Cirrincione, C. T., Sikov, W. M., Berry, D. A., Jasinski, S., Weisberg, T. F., Somlo, G., Hudis, C., Winer, E., Ollila, D. W., Impact of neoadjuvant chemotherapy in stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation rates: Surgical results from CALGB 40603 (Alliance), Annals of Surgery, 262, 434-438, 2015	Same trial as Sikov. Outcome is breast conservation rates
Guan, X., Ma, F., Fan, Y., Zhu, W., Hong, R., Xu, B., Platinum-based chemotherapy in triple-negative breast cancer: A systematic review and meta-analysis of randomized-controlled trials, Anti-Cancer Drugs, 26, 894-901, 2015	Systematic review without any additional RCTs
Guarneri, V., Dieci, M. V., Bisagni, G., Boni, C., Cagossi, K., Puglisi, F., Pecchi, A., Piacentini, F., Conte, P., Preoperative carboplatin-paclitaxel-bevacizumab in triple-negative breast cancer: final results of the phase II Ca.Pa.Be study, Annals of Surgical Oncology, 22, 2881-7, 2015	Not randomized study
Kaklamani, V. G., Jeruss, J. S., Hughes, E., Siziopikou, K., Timms, K. M., Gutin, A., Abkevich, V., Sangale, Z., Solimeno, C., Brown, K. L., Jones, J., Hartman, A. R., Meservey, C., Jovanovic, B., Helenowski, I., Khan, S. A.,	No randomization

Excluded studies - RQ10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neo-adjuvant chemotherapy?	
Study	**Reason for exclusion**
Bethke, K., Hansen, N., Uthe, R., Giordano, S., Rosen, S., Hoskins, K., Von Roenn, J., Jain, S., Parini, V., Gradishar, W., Phase II neoadjuvant clinical trial of carboplatin and eribulin in women with triple negative early-stage breast cancer (NCT01372579), Breast Cancer Research & TreatmentBreast Cancer Res Treat, 151, 629-38, 2015	
Kern, P., Kalisch, A., von Minckwitz, G., Putter, C., Kolberg, H. C., Pott, D., Kurbacher, C., Rezai, M., Kimmig, R., Neoadjuvant, anthracycline-free chemotherapy with carboplatin and docetaxel in triple-negative, early-stage breast cancer: a multicentric analysis of rates of pathologic complete response and survival, Journal of ChemotherapyJ Chemother, 28, 210-7, 2016	No randomization
Liedtke, C., Gluz, O., Nitz, U., Christgen, M., Sotlar, K., Grischke, E. M., Forstbauer, H., Braun, M., Warm, M., Hackmann, J., Uleer, C., Aktas, B., Schumacher, C., Bangemann, N., Linder, C., Kummel, S., Clemens, M., Potenberg, J., Peter, S., Kohls, A., Pelz, E., Kates, R. E., Wurstlein, R., Kreipe, H., Harbeck, N., Comparison of 12 weeks neoadjuvant Nab-paclitaxel combined with carboplatinum vs. Gemcitabine in triple negative breast cancer: WSG-ADAPT TN randomized phase II trial, Oncology Research and Treatment, 39, 53, 2016	Conference abstract
Liu, M., Mo, Q. G., Wei, C. Y., Qin, Q. H., Huang, Z., He, J., Platinum-based chemotherapy in triple-negative breast cancer: A meta-analysis, Oncology Letters, 5, 983-991, 2013	Systematic review with palliative and neoadjuvant therapy. No additional RCTs
Martinez, Mca, Arce-Salinas, C, Alvarado-Miranda, A, Lara-Medina, F, Flores-Diaz, D, Matus, Ja, Bargallo-Rocha, E, Shaw-Dulin, R, Maldonado, H, Mendoza-Galindo, L, Perez-Sanchez, V, Randomized phase II trial to evaluate the safety and efficacy of neoadjuvant cisplatin in combination with taxanesanthracyclines vs taxanesanthracyclines alone in locally advanced triple negative breast cancer, Journal of Clinical Oncology, 33, 2015	Exclusion by publication type: Meeting Abstract
Minckwitz, G, Schneeweiss, A, Loibl, S, Salat, C, Denkert, C, Rezai, M, Blohmer, Ju, Jackisch, C, Paepke, S, Gerber, B, Zahm, Dm, Kümmel, S, Eidtmann, H, Klare, P, Huober, J, Costa, S, Tesch, H, Hanusch, C, Hilfrich, J, Khandan, F, Fasching, Pa, Sinn, Bv, Engels, K, Mehta, K, Nekljudova, V, Untch, M, Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial, The Lancet. Oncology, 15, 747-56, 2014	Exclusion by publication type. This is abstract. Full text article included in review
Minckwitz, G, Schneeweiss, A, Salat, C, Rezai, M, Zahm, Dm, Klare, P, Blohmer, Ju, Tesch, H, Khandan, F, Jud, S, Jackisch, C, Mehta, K, Loibl, S, A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto), Journal of clinical oncology, 31, 2013	Multiple reports of an included study
Najafi, S., Payandeh, M., Sadeghi, M., Shafaei, V., Shojaiyan, F., Abbasvandi, F., Phase II study of adjuvant docetaxel and carboplatin with/without doxorubicin and cyclophosphamide in triple negative breast cancer: A randomised controlled clinical trial, Wspolczesna Onkologia, 21, 83-89, 2017	Exclusion by intervention: Both arms receiving Carboplatin therapy

Excluded studies - RQ10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neo-adjuvant chemotherapy?	
Study	**Reason for exclusion**
Nasr, K. E., Osman, M. A., Elkady, M. S., Ellithy, M. A., Metronomic methotrexate and cyclophosphamide after carboplatin included adjuvant chemotherapy in triple negative breast cancer: a phase III study, Annals of Translational Medicine, 3, 284, 2015	Comparison between maintenance therapy, not neoadjuvant chemotherapy
Petrelli, F., Coinu, A., Borgonovo, K., Cabiddu, M., Ghilardi, M., Lonati, V., Barni, S., The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: A systematic review and meta-analysis, Breast Cancer Research and Treatment, 144, 223-232, 2014	Systematic review with no additional RCTs
Rugo, Hs, Olopade, Oi, DeMichele, A, Yau, C, t, Veer Lj, Buxton, Mb, Hogarth, M, Hylton, Nm, Paoloni, M, Perlmutter, J, Symmans, Wf, Yee, D, Chien, Aj, Wallace, Am, Kaplan, Hg, Boughey, Jc, Haddad, Tc, Albain, Ks, Liu, Mc, Isaacs, C, Khan, Qj, Lang, Je, Viscusi, Rk, Pusztai, L, Moulder, Sl, Chui, Sy, Kemmer, Ka, Elias, Ad, Edmiston, Kk, Euhus, Dm, Haley, Bb, Nanda, R, Northfelt, Dw, Tripathy, D, Wood, Wc, Ewing, C, Schwab, R, Lyandres, J, Davis, Se, Hirst, Gl, Sanil, A, Berry, Da, Esserman, Lj, Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer, New England journal of medicine, 375, 23-34, 2016	Bayesian probability of pCR reported rather than raw data
Severson, T. M., Wolf, D. M., Yau, C., Peeters, J., Wehkam, D., Schouten, P. C., Chin, S. F., Majewski, I. J., Michaut, M., Bosma, A., Pereira, B., Bismeijer, T., Wessels, L., Caldas, C., Bernards, R., Simon, I. M., Glas, A. M., Linn, S., van't Veer, L., The BRCA1ness signature is associated significantly with response to PARP inhibitor treatment versus control in the I-SPY 2 randomized neoadjuvant setting, Breast Cancer Research, 19 (1) (no pagination), 2017	Outcomes outside scope: gene signature development
Sharma, P, PARP inhibitor and platinum agent in triple negative breast cancer: utilizing innovative trial design to bring together something "new" and something "old", Chinese Clinical OncologyChin, 6, 2017	Narrative review
Sharma, P, Lopez-Tarruella, S, Garcia-Saenz, Ja, Ward, C, Connor, Cs, Gomez, Hl, Prat, A, Moreno, F, Jerez-Gilarranz, Y, Barnadas, A, Picornell, Ac, Monte-Millan, M, Gonzalez-Rivera, M, Massarrah, T, Pelaez-Lorenzo, B, Palomero, Mi, Gonzalez, Del Val R, Cortes, J, Rivera, Hf, Morales, Db, Marquez-Rodas, I, Perou, Cm, Wagner, Jl, Mammen, Jmv, McGinness, Mk, Klemp, Jr, Amin, Al, Fabian, Cj, Heldstab, J, Godwin, Ak, Jensen, Ra, Kimler, Bf, Khan, Qj, Martin, M, Efficacy of neoadjuvant carboplatin plus docetaxel in triple-negative breast cancer: combined analysis of two cohorts, Clinical Cancer Research, 23, 649-657, 2017	Not randomized study
Tian, M., Zhong, Y., Zhou, F., Xie, C., Zhou, Y., Liao, Z., Platinum-based therapy for triple-negative breast cancertreatment: A meta-analysis, Molecular and Clinical Oncology, 3, 720-724, 2015	Metaanalysis with no additional RCTs
Valsecchi, M. E., Kimmey, G., Bir, A., Silbermins, D., Role of Carboplatin in the Treatment of Triple Negative Early- Stage Breast Cancer, Reviews on Recent Clinical TrialsRev Recent Clin Trials, 10, 101-10, 2015	Review article without additional studies
Vollebergh, M. A., Lips, E. H., Nederlof, P. M., Wessels, L. F. A., Schmidt, M. K., van Beers, E. H., Cornelissen, S., Holtkamp, M., Froklage, F. E., de Vries, E. G. E., Schrama, J. G., Wesseling, J., van de Vijver, M. J., van Tinteren, H., de Bruin, M., Hauptmann, M., Rodenhuis, S., Linn, S. C., An aCGH classifier derived from BRCA1-mutated breast cancer and benefit of high-dose platinum-based chemotherapy in HER2-negative breast cancer patients, Annals of Oncology, 22, 1561-1570, 2011	Exclusion b population: Not early breast cancer. Patients with metastasis

Excluded studies - RQ10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neo-adjuvant chemotherapy?	
Study	**Reason for exclusion**
Wang, L. Y., Xie, H., Zhou, H., Yao, W. X., Zhao, X., Wang, Y., Efficacy of carboplatin-based preoperative chemotherapy for triple-negative breast cancer: A meta-analysis of randomized controlled trials, Saudi Medical Journal, 38, 18-23, 2017	Systematic review without additional RCTs
Yuan, P., Xu, B., A phase III, randomized trial of docetaxel plus carboplatin (TP) versus epirubicin plus cyclophosphamide followed by docetaxel (EC-T) as adjuvant treatment for triple-negative, early-stage breast cancer in Chinese patients, Journal of Clinical Oncology, 30, no pagination, 2012	This is a study protocol. Results are not available.

EBC, early breast cancer; pCR, pathologically complete response; RCT, randomised controlled trial;

Economic studies

See Supplement 1: Health economics literature review for list of excluded economic studies.

Appendix L – Research recommendations

Research recommendations for 10.1 What is the effectiveness of neoadjuvant chemotherapy?

No research recommendations were made for this question.

Research recommendations for 10.2 Is there a benefit for neoadjuvant endocrine therapy for people with early and locally advanced breast cancer?

Research recommendation: Is neoadjuvant endocrine therapy safe in premenopausal women with early breast cancer?

Why this is important

Endocrine therapy is an established part of adjuvant treatment for breast cancer in women with oestrogen receptor (ER)-positive disease. It reduces local and distant recurrence and reduces the risk of new breast cancers.

Endocrine therapy is well tolerated and safe to deliver as an outpatient treatment, does not need invasive monitoring, and needs less intensive visit schedules than neoadjuvant chemotherapy.

Endocrine therapy has been shown to achieve tumour shrinkage when used as first-line treatment (before surgery). However, in premenopausal women, this response was only identified in a proportion of women and evidence came from a single small study.

Although neoadjuvant chemotherapy is effective in achieving tumour shrinkage, not all premenopausal women need chemotherapy, and therefore neoadjuvant endocrine therapy may be an alternative.

No evidence was identified to confirm the long-term safety of neoadjuvant endocrine therapy in premenopausal women or to indicate which premenopausal women will benefit from it to achieve tumour shrinkage, and so research is needed to ascertain this.

Table 24: Research recommendation rationale

Research question	Is neoadjuvant endocrine therapy safe in premenopausal women with early breast cancer?
Importance to 'patients' or the population	In some women neoadjuvant endocrine therapy can facilitate tumour shrinkage and therefore breast conserving surgery (BCS). BCS is in general more acceptable to patients with improved patient reported outcomes compared to mastectomy, and even relatively small tumours may have increased surgical breast conserving (oncoplastic) options with better long term cosmesis (patient reported outcomes) if tumour shrinkage is achieved. Endocrine therapy is a less toxic alternative to chemotherapy to achieve tumour shrinkage, requires less intensive and less invasive monitoring. In order to effectively counsel patients good quality evidence is required in premenopausal women to confirm that neoadjuvant endocrine therapy plus BCS plus radiotherapy has equivalent oncological outcomes (disease-free survival, local recurrence rate and overall survival) to the alternatives: Neoadjuvant chemotherapy to achieve tumour shrinkage plus BCS plus radiotherapy Mastectomy +/- reconstruction More extensive (and potentially less cosmetic) BCS options A potential benefit to the patient of knowing chemo plan early in treatment pathway
Relevance to NICE guidance	Generally low quality evidence for neoadjuvant chemotherapy identified. Only low or moderate quality evidence identified in defined premenopausal age group. Only report on clinical changes in tumour size specifically for premenopausal women.

Research question	Is neoadjuvant endocrine therapy safe in premenopausal women with early breast cancer?
	No evidence identified specific to premenopausal women for other outcomes including overall survival and radiological change in tumour size.
Relevance to the NHS	Neoadjuvant endocrine therapy is cost-effective compared to neoadjuvant chemotherapy, requires less intensive and less invasive monitoring for side-effects and toxicity. Endocrine therapy will already be part of the adjuvant treatment and proposed regimen alters the timing of therapy but not the cost. BCS is cheaper and more efficient than mastectomy plus reconstruction with lower complication rates. Potential cost saving.
National priorities	Evidence based healthcare Increased surgical (oncoplastic) options for women if tumour shrinkage is achieved Association of Breast Surgery aim: every patient in a trial Achieving world class cancer outcomes: A strategy for England 2015-2020 Improving outcomes strategy for cancer (2011) Cancer reform strategy (2007) National cancer survivorship initiative (2010)
Current evidence base	Lack of evidence for premenopausal women, including: Which premenopausal women respond to neoadjuvant endocrine therapy Safety data (disease-free survival, local recurrence rate and overall survival) Optimum regimens or expected duration of therapy to achieve maximum shrinkage
Equality	Men cannot be premenopausal. Men are surgically treated with mastectomy and therefore a trial with outcome (tumour shrinkage and BCS) is not appropriate.

BCS, breast conserving surgery

Table 25: Research recommendation modified PICO table

Criterion	Explanation
Population	Premenopausal women ER-positive HER2-negative Invasive breast cancer Risk assessed to not require chemotherapy (current NICE approved option for risk assessment is Oncotype) Clinically and/or radiologically measurable. T1-3, N0-1 clinically/radiologically
Intervention	Neoadjuvant endocrine therapy (tamoxifen or goserelin plus an aromatase inhibitor) At least 6 months neoadjuvant endocrine therapy continued up to 12 months (or 2 years) if continuing radiological shrinkage
Comparator (without the risk factor)	• Surgery without neoadjuvant endocrine therapy
Outcome	• Response rates including: • Reduction in tumour size (clinical and radiological) • Pathological complete response rates, • Pathological partial response rates • Breast conservation rates (procedure type) • Excision volumes

Criterion	Explanation
	• Re-excision rates • Time to maximum shrinkage • Safety data: • Disease-free survival (at 5 years) • Local (in breast) recurrence rates (at 5 years) • Overall survival (at 5 years) • Adverse events (disease progression, thromboembolic and menopausal side effects) • PROMS / QoL study – including menopausal side-effects • Biomarker testing or tumour sub-typing may help identify which women will respond to neoadjuvant endocrine therapy so include a biomarker sub-study
Study design	Randomised
Timeframe	5 years for oncological safety data 1 -2 years for reduction in tumour size and BCS rates

ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; NICE, National Institute of Health and Care Excellence; PROMS, patient-reported outcome measures; QoL, quality of life

Research recommendation: Is there a benefit for neoadjuvant endocrine therapy in postmenopausal women with early breast cancer?

Why this is important

Endocrine therapy is an established part of adjuvant treatment for breast cancer in women with oestrogen receptor-positive disease. It reduces local and distant recurrence and reduces the risk of new breast cancers.

Endocrine therapy is well tolerated and safe to deliver as an outpatient treatment, does not need invasive monitoring, and needs less intensive visit schedules than neoadjuvant chemotherapy.

Endocrine therapy has been shown to achieve tumour shrinkage when used as first-line treatment (before surgery). However, in the postmenopausal women subgroup, the evidence was of low quality.

While neoadjuvant chemotherapy is an effective option to achieve tumour shrinkage, not all postmenopausal women need or may benefit from chemotherapy, and therefore neoadjuvant endocrine therapy may be an alternative. Research is needed to determine if this is the case.

Table 26: Research recommendation rationale

Research question	Is there a benefit for neoadjuvant endocrine therapy for postmenopausal women with early breast cancer?
Importance to 'patients' or the population	In some women neoadjuvant endocrine therapy can facilitate tumour shrinkage and therefore breast conserving surgery (BCS). BCS is in general more acceptable to patients with improved patient reported outcomes compared to mastectomy. Even relatively small tumours may have increased surgical breast conserving (oncoplastic) options with better long term cosmesis (patient reported outcomes) if tumour shrinkage is achieved. Neoadjuvant endocrine therapy is a less toxic alternative to neoadjuvant chemotherapy to achieve tumour shrinkage. Neoadjuvant endocrine therapy requires less intensive and less invasive monitoring.

Research question	Is there a benefit for neoadjuvant endocrine therapy for postmenopausal women with early breast cancer?
	In order to effectively counsel patients good quality evidence is required in postmenopausal women to confirm that neoadjuvant endocrine therapy plus BCS plus radiotherapy has equivalent oncological outcomes (disease-free survival, local recurrence rate and overall survival) to the alternatives: Neoadjuvant chemotherapy to achieve tumour shrinkage plus BCS plus radiotherapy Mastectomy +/- reconstruction More extensive (and potentially less cosmetic) BCS options
Relevance to NICE guidance	Generally low quality evidence for neoadjuvant endocrine therapy identified. Only low quality evidence identified in defined postmenopausal sub group.
Relevance to the NHS	Neoadjuvant endocrine therapy is cost-effective compared to neoadjuvant chemotherapy. Neoadjuvant endocrine therapy requires less intensive and less invasive monitoring for side-effects and toxicity. Endocrine therapy will already be part of the adjuvant treatment and proposed regimen alters the timing of therapy but not the cost. Breast conserving surgery is cheaper and more efficient than mastectomy plus reconstruction with lower complication rates. Potential cost saving.
National priorities	Evidence based healthcare Increased surgical (oncoplastic) options for women if tumour shrinkage is achieved Association of Breast Surgery aim: every patient in a trial Achieving world class cancer outcomes: A strategy for England 2015-2020 Improving outcomes strategy for cancer (2011) Cancer reform strategy (2007) National cancer survivorship initiative (2010)
Current evidence base	Lack of high quality evidence for postmenopausal women Including: Which women respond to neoadjuvant endocrine therapy Response rates. Safety data (disease-free survival, local recurrence rates) Optimum regimens or expected duration of therapy to achieve maximum shrinkage
Equality	Men are surgically treated with mastectomy and therefore a trial with outcomes including (tumour shrinkage and BCS) is not appropriate.

BCS, breast conserving surgery

Table 27: Research recommendation modified PICO table

Criterion	Explanation
Population	Postmenopausal women ER-positive HER2-negative Invasive breast cancer Risk assessed to not definitely require chemotherapy Clinically and/or radiologically measurable. T1-3, N0-1 clinically/radiologically
Intervention	Neoadjuvant endocrine therapy (aromatase inhibitor) At least 6 months neoadjuvant endocrine therapy continued up to 12 months (or 2 years) if continuing radiological shrinkage

Criterion	Explanation
Comparator (without the risk factor)	• Surgery without neoadjuvant therapy • Neoadjuvant chemotherapy
Outcome	• Response rates including: • Reduction in tumour size (clinical and radiological) • Pathological complete response rates, • Pathological partial response rates • Breast conservation rates (procedure type) • Excision volumes • Re-excision rates • Time to maximum shrinkage • Safety data: • Disease-free survival (at 5 years) • Local (in breast) recurrence rates (at 5 years) • Overall survival (at 5 years) • Adverse events (disease progression, menopausal side-effects) • PROMS / QOL study – including menopausal side-effects • Biomarker testing or tumour sub-typing may help identify which women will respond to neoadjuvant endocrine therapy so include a biomarker sub-study
Study design	Randomised
Timeframe	5 years for oncological safety data 1 -2 years for reduction in tumour size and BCS rates

ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; NICE, National Institute of Health and Care Excellence; PROMS, patient-reported outcome measures; QoL, quality of life

Research recommendations for 10.3 What are the indications for post mastectomy radiotherapy following neoadjuvant systemic therapy?

Research recommendation: What are the indications for postmastectomy radiotherapy after neoadjuvant chemotherapy?

Why this is important

Neoadjuvant chemotherapy is being increasingly used for selected groups of people with early breast cancer. The results of this approach have improved dramatically over recent years with up to 50–60% of people now showing a complete pathological response. Postoperative radiotherapy is generally recommended for women who have mastectomy after neoadjuvant chemotherapy because currently, available data do not permit people to be identified for whom radiotherapy could be safely omitted.

Complete pathological response has been shown to correlate with improved disease-free survival in women with ER-negative or human epidermal growth receptor 2 (HER2)-positive disease. It is therefore likely that women whose disease responds well to preoperative treatment will also derive less benefit from radiotherapy. Potentially, the toxicity of radiotherapy (cardiac damage, second malignancies) may outweigh the benefits in this subgroup. A randomised controlled trial is needed to test this hypothesis.

Table 28: Research recommendation rationale

Research question	What are the indications for postmastectomy radiotherapy following neoadjuvant chemotherapy?
Importance to 'patients' or the population	High. If postmastectomy radiotherapy is not of benefit then it can be omitted, sparing women additional toxicity and inconvenience. Omission of radiotherapy will also improve the cosmetic outcome of any subsequent reconstructive surgery
Relevance to NICE guidance	High. Current NICE guidance has identified this as a knowledge gap
Relevance to the NHS	High. The number of people having neoadjuvant systemic therapy is growing. Furthermore improvements in the effectiveness of this will increase the number of people whose treatment would be informed by this research. At present women are generally recommended to receive post mastectomy radiotherapy irrespective of tumour response. If this is proven to be unnecessary then there would be a considerable cost saving to the NHS.
National priorities	Achieving world class cancer outcomes: A strategy for England 2015-2020 Improving outcomes strategy for cancer (2011) Cancer reform strategy (2007) National cancer survivorship initiative (2010)
Current evidence base	NSABP B51 trial is asking the same question. Start date August 2013. Completion estimated 2023. Estimated enrolment is 1636 of which approximately half will have mastectomy. It is unlikely that this trial will by itself confirm non-inferiority and answer this question definitively
Equality	Breast cancer affects a wide cross section of the population. The research sample and provision of support and information should reflect this diversity, and be tailored to meet individual needs.

Table 29: Research recommendation modified PICO table

Criterion	Explanation
Population	Women treated with mastectomy who have received neoadjuvant chemotherapy with a complete pathological response

Criterion	Explanation
Intervention	Chest wall radiotherapy and regional nodal irradiation
Comparator	• No chest wall radiotherapy
Outcomes	• Locoregional recurrence, disease-free survival, overall survival • Stratify by ER status, HER2 status, pre-op clinical stage
Study design	Randomised controlled trial
Timeframe	10 year follow-up

ER, oestrogen receptor; HER2, Human epidermal growth factor receptor 2

Research recommendations for 10.5 Do people with triple negative or BRCA germ line mutation with early and locally advanced breast cancer benefit from the addition of a platinum to anthracycline (± taxanes) based neoadjuvant chemotherapy?

No research recommendations were made for this question.