National Institute for Health and Care Excellence

Draft for Consultation

Early and locally advanced breast cancer: diagnosis and management

[E] Evidence reviews for adjuvant chemotherapy

NICE guideline tbc

Evidence reviews

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

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Adjuvant chemotherapy

This Evidence Report contains information on 1 review relating to adjuvant chemotherapy.

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Review question 5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline- based adjuvant chemotherapy?

Introduction

Adjuvant chemotherapy for early breast cancer is given after surgery to reduce local and distant disease recurrence by reducing microscopic disease burden that could potentially grow and cause disease relapse in the future. Adjuvant chemotherapy is recommended when there is sufficient risk from breast cancer recurrence and the decision to use adjuvant therapy will be based on a balance between the benefits and risks of chemotherapy, particularly in people with comorbidities.

Adjuvant chemotherapy schedules have developed over a number of years with trials examining the benefits of adding specific classes of drugs, as well as varying the delivery schedules (for example 'standard' versus 'dose-dense' regimens when treatment is given over shorter intervals).

Anthracycline-based chemotherapy is the backbone of most adjuvant chemotherapy regimens with taxanes added in higher risk disease. The previous guideline CG80 (NICE 2009) on early and locally advanced breast cancer only recommended the addition of docetaxel in node-positive breast cancer. However, there is now new evidence that suggests the benefit of combination anthracycline and taxane-containing regimens is not just based on stage but may also be related to the phenotype of disease.

The aim of this review is to define which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline-based adjuvant chemotherapy.

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 early or locally advanced breast cancer who have undergone breast surgery and are suitable for anthracycline-based adjuvant chemotherapy
Intervention	Taxane- (docetaxel and paclitaxel) containing regimen
Comparison	Non-taxane-containing regimen
Outcome	**Critical** • Overall survival • Disease-free survival • Treatment-related morbidity **Important** • Adequate dose intensity • 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

Twenty-eight articles (number of participants, N=135,285) were included in the review (Albert 2011; Brain 2005; Coombes 2011; Coudert 2012; Delbaldo 2014; Del Masteo 2016; Early Breast Cancer Trialists' Collaborative, Group 2012; Ellis 2009; Francis 2008; Gianni 2009; Henderson 2003; Jacquemier 2011; Janni 2016; Kummel 2006; Mackey 2013; Mamounas 2005; Martin 2008; Martin, Rodriguez-Lescure 2010; Martin, Segui 2010; Martin 2013; Nitz 2014; Oakman 2013; Polyzos 2010; Roche 2006; Roy 2012; Sakr 2013; Schwentner 2016; Vici 2012). These trials reported evidence from 22 randomised controlled trials (RCTs; ADEBAR [number of publications, k=2], Association Europèenne de Recherche en Oncologie [AERO]-B2000 [k=1], Albert 2011 [k=1], Breast Cancer International Research Group [BCIRG] 001 [k=1], BIG 02-98 [k=2], Cancer and Leukemia Group B [CALGB] 9344 [k=1], docetaxel epirubicin adjuvant trial [DEVA; k=1], epirubicin docetaxel trial [EC-Doc] [k=1], European Cooperative Trial in Operable Breast Cancer [ECTO; k=1], Grupo Español de Investigación en Cáncer de Mama [GEICAM] 2003-02 [k=1], GEICAM 9805 [k=1], GEICAM 9906 [k=2], Gruppo Oncologico Italia Meridionale [GOIM] 9902 [k=1], Gruppo Oncologico Nord-Ovest - Mammella Intergruppo Group 5 [GONO-MIG5; k=1], Hellenic Oncology Research Group [HORG; k=1], Kummel 2006 [k=1], National Surgical Adjuvant Breast and Bowel Project [NSABP] B-28 [k=1], PACS 01 [k=3], Risk Assessment and Prevention Program [RAPP] 01 [k=1], Roy 2012 [k=1], Sakr 2013 [k=1], TACT [k=1]) and 1 systematic review of RCTs. The systematic review reported individual patient data from 123 trials; however, only the following trials were consistent with the review protocol: ADEBAR, BCIRG001, BIG 02-98, CALGB 9344, DEVA, EC-Doc, ECOG E2197, ECTO, HORG, GOIM 9805, GOIM 9902, GOIM 9906, GONO MIG5, MD Anderson, NNCBC 3-Europe, NSAPB B-28, PACS 01, PACS 04, RAPP-01, TACT, Taxit216. Where the evidence reported in the published systematic review covered a larger sample, longer follow-up period, or an additional subgroup of interest compared to the evidence reported in the published articles identified above this evidence data was included in the guideline analysis.

Four trials compared epirubicin and cyclophosphamide (EC) and docetaxel against fluorouracil, epirubicin and cyclophosphamide (FEC); 2 trials compared docetaxel, doxorubicin and cyclophosphamide (TAC) against fluorouracil, doxorubicin and cyclophosphamide (FAC); 7 trials compared FEC or FAC and docetaxel or paclitaxel against FEC or FAC alone; 1 trial compared epirubicin and docetaxel/paclitaxel against FEC; 1 trial compared doxorubicin and docetaxel against doxorubicin and cyclophosphamide (AC); 1 trial compared epirubicin and docetaxel against epirubicin alone; and 3 trials compared doxorubicin or epirubicin and docetaxel or paclitaxel and cyclophosphamide, methotrexate and fluorouracil (CMF) against doxorubicin or epirubicin (with or without cyclophosphamide) and CMF. Data from the published systematic review was incorporated into the guideline review for the following comparisons: FEC/FAC and docetaxel/paclitaxel versus FEC/FAC; AC/EC and paclitaxel/docetaxel versus AC/EC; epirubicin and docetaxel/paclitaxel versus FEC; doxorubicin and docetaxel versus AC; and doxorubicin/epirubicin and docetaxel/paclitaxel and CMF versus doxorubicin/epirubicin (with or without cyclophosphamide) and CMF.

Seventeen trials (ADEBAR; AERO-B2000; Albert 2011; BCIRG 001; BIG 02-98; CALGB 9344; DEVA; EC-Doc; GEICAM 2003-02; GEICAM 9805; GOIM 9902; GONO-MIG5; HORG; Kummel 2006; NSABP B-28; PACS 01; Roy 2012; TACT) reported data for critical outcomes

by subgroups of interest: node negative (k=3), node positive (k=16), T stage 1 (k=5), T stage 2 (k=2), ER+ (k=6), ER- (k=5), HER2+ (k=7), HER2- (k=6), triple negative (k=5), aged <60 years (k=2), aged ≥60 years (k=2). Additionally, 1 trial reported data for T stage 1 and 2 combined, 1 trial reported data for T stage 2 and 3 combined, 2 trials reported data for T stage 2+, and 3 trials reported data for T stage 3+. There was no subgroup data available for participants with cardiac disease, or based on performance status.

The clinical studies included in this evidence review are summarised in Table 2 and evidence from these is summarised in the clinical GRADE evidence profiles below (Table 3 to Table 9). 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 2: Summary of included studies

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Albert 2011	No trial name	• T1-3; N0-1; adequate bone marrow, liver and renal function • Exclusion: uncompensated congestive heart failure; previous invasive cancer (except cervical and skin cancer)	Intervention arm: 4 x 21-day cycles of paclitaxel followed by 4 cycles of FAC Control arm: 8 cycles of FAC
Brain 2005	RAPP 01	• Women aged 18-70; surgery with axillary dissection and clear margins; high risk node negative or limited (≤3) node positive	Intervention arm: 4 cycles of doxorubicin and docetaxel Control arm: 4 cycles of AC
Coombes 2011	DEVA	• Post-menopausal women; node positive; normal hematologic, hepatic, renal and cardiac function • Exclusion: history of malignancy	Intervention arm: 3 x 28-day cycles of epirubicin followed by 3 21-day cycles of docetaxel Control arm: 6 x 28-day cycles of epirubicin
Coudert 2012	PACS01	• Women aged 18-64; node positive unilateral breast cancer; surgery with axillary dissection and clear margins; WHO performance status <2; adequate renal, hepatic and cardiac function • Exclusion: cardiac disease	Intervention arm: 3 x 21-day cycles of FEC followed by 3 x 21-day cycles of docetaxel Control arm: 6 x 21-day cycles of FEC

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		contraindicating anthracycline use	
Delbaldo 2014	B2000	• Women aged >17; WHO performance score ≤2; node positive; adequate hematologic function • Exclusion: prior chemotherapy or radiotherapy; bilateral, inflammatory or contralateral breast cancer; cardiac history; pregnant or breastfeeding; history of malignancy; life expectancy < 2 years; contraindications to study drugs; psychiatric morbidity; participating in other trial(s)	Intervention arm: 4 x 21-day cycles of FEC followed by 4 x 21-day cycles of paclitaxel Control arm: 6 x 21-day cycles of FEC
Del Mastro 2016	GONO-MIG5	• Surgery with axillary dissection and clear margins; 1-10 involved axillary lymph nodes; aged <70; adequate hematologic, hepatic and renal function • Exclusion: prior chemoerapy	Intervention arm: 4 x 21-day cycles of EP Control arm: 6 x 21-day cycles of FEC
Early Breast Cancer Trialists' Collaborative, Group 2012	ADEBAR, BCIRG001, BIG 02-98, CALGB 9344, DEVA, EC-Doc, ECOG E2197, ECTO, HORG, GOIM 9805, GOIM 9902, GOIM 9906, GONO MIG5, MD Anderson, NNCBC 3-Europe, NSAPB B-28, PACS 01, PACS 04, RAPP-01, TACT, Taxit216	• All randomised trials that began 1973 to 2003 and compared taxane-based and non-taxane based regimens	Interventions grouped into taxane-plus-anthracycline-based regimen vs. the same non-taxane cytotoxic chemotherapy, taxane-plus-anthracycline-based regimen (taxane given sequentially) vs. more (but <doubled) non-taxane cytotoxic chemotherapy, taxane-plus-anthracycline-based regimen (taxane given concurrently) vs. more (but <doubled) non-taxane cytotoxic chemotherapy and taxane-plus-anthracycline-based regimen vs. doubled non-taxane cytotoxic chemotherapy
Ellis 2009	TACT	• Surgery with clear margins; node-positive or high-risk node-negative; normal hematologic, hepatic and renal function • Exclusion: locally advanced or bilateral breast cancer;	Intervention arm: 4 x 21-day cycles of FEC followed by 4 x 21-day cycles of docetaxel Control arm: 8 x 21-day cycles of FEC

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		pregnant; other invasive malignancy in last 10 years	
Francis 2008	BIG 02-98	• Aged 18-70; node positive; clear surgical margins; adequate hematologic, renal, liver and cardiac function • Exclusion: supraclavicular node involvement; previous cancer; grade 2+ neuropathy; serious comorbidities	Intervention arms: 1) 3 x 21-day cycles of doxorubicin followed by 3 x 21-day cycles of docetaxel followed by 3 cycles of CMF; 2) 4 x 21-day cycles of doxorubicin and docetaxel followed by 3 x 21-day cycles of CMF Control arms: 1) 4 x 21-day cycles of doxorubicin followed by 3 cycles of CMF; 2) 4 x 21-day cycles of doxorubicin and cyclophosphamide followed by 3 cycles of CMF
Gianni 2009	ECTO	• Tumour >2cm in diameter; known hormonal receptor status and grade; Karnofsky performance status >70; adequate bone marrow, renal, liver and cardiac function; normal blood pressure • Exclusion: pregnant or breastfeeding; prior cancer; cardiac arrhythmias, congestive heart failure or myocardial infarction; active infection; pre-existing neuropathy; psychiatric disorder preventing informed consent	Intervention arm: 4 x 21-day cycles of doxorubicin and paclitaxel followed by 4 x 28-day cycles of CMF Control arm: 4 x 21-day cycles of doxorubicin followed by 4 x 28-day cycles of CMF
Henderson 2003	CALGB 9344	• Surgery with axillary dissection and clear margins; involved axillary lymph nodes	Intervention arm: 4 x 21-day cycles of AC followed by 4 x 21-day cycles of paclitaxel Control arm: 4 x 21-day cycles of AC
Jacquemier 2011	PACS01	• Women aged 19-64; node positive; surgery with axillary dissection and clear margins; WHO performance status <2; adequate renal, hepatic and cardiac function • Exclusion: cardiac disease contraindicating anthracycline use	Intervention arm: 3 x 21-day cycles of FEC followed by 3 x 21-day cycles of docetaxel Control arm: 6 x 21-day cycles of FEC

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Janni 2016	ADEBAR	• Women aged 18-70; at least 4 involved axillary lymph nodes; surgery with axillary dissection and clear margins; ECOG performance status <2; adequate bone marrow reserve; adequate renal and liver function; life expectancy ≥32 weeks • Exclusion: inflammatory breast cancer; previous cancer treatment; previous malignancy (other than cervical or skin cancer); cardiac morbidities affecting left ventricular function; myocardial infarction, angina pectoris or uncontrolled arterial hypertension within last 6 months; pregnant or breastfeeding; hypersensitivity to study medications	Intervention arm: 4 x 21-day cycles of EC followed by 4 x 21-day cycles of docetaxel Control arm: 6 x 28-day cycles of FEC
Kummel 2006	No trial name	• Surgery with axillary dissection and clear margins; at least 4 involved axillary lymph nodes; ECOG performance status <2; adequate organ function and bone marrow reserve • Exclusion: previous chemotherapy or radiotherapy	Intervention arm: 4 x 14-day cycles of epirubicin and paclitaxel followed by 3 x 14-day cycles of CMF Control arm: 4 x 21-day cycles of epirubicin and cyclophosphamide followed by 3 x 21-day cycles of CMF
Mackey 2013	BCIRG001	• Women aged 18-70; Karnofsky performance scale score ≥80%; surgery with axillary dissection and clear margins; positive axillary node involvement	Intervention arm: 6 x 21-day cycles of TAC Control arm: 6 x 21-day cycles of FAC
Mamounas 2005	NSABP B-28	• Lumpectomy (and axillary dissection) with clear margins or modified radical mastectomy; node positive; adequate hematologic, hepatic	Intervention arm: 4 x 21-day cycles of AC followed by 4 x 21-day cycles of paclitaxel Control arm: 4 x 21-day cycles of AC

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		and renal function; ≥10 year life expectancy • Exclusion: previous history of breast cancer; prior radiotherapy, chemotherapy, immunotherapy or hormonal therapy for breast cancer	
Martin 2008	GEICAM 9906	• Women aged 18-75; surgery with axillary dissection and clear margins; adequate bone marrow, liver and renal function • Exclusion: advanced disease; history of cancer; grade 2+ neuropathy; pregnant or lactating; serious comorbidities	Intervention arm: 4 x 21-day cycles of FEC followed by 8 weekly cycles of paclitaxel Control arm: 6 x 21-day cycles of FEC
Martin 2010a	GEICAM 9906	• Women aged 18-75; surgery with axillary dissection and clear margins; adequate bone marrow, lover and renal function • Exclusion: advanced disease; history of cancer; grade 2+ neuropathy; pregnant or lactating; serious comorbidities	Intervention arm: 4 x 21-day cycles of FEC followed by 8 weekly cycles of paclitaxel Control arm: 6 x 21-day cycles of FEC
Martin 2010b	GEICAM 9805	• Women aged 18-70; negative axillary lymph nodes; meet at least 1 of the 1998 St. Gallen high risk criteria	Intervention arm: 6 x 21-day cycles of TAC Control arm: 6 x 21-day cycles of FAC
Martin 2013	GEICAM/2003-02	• Aged 18-70; negative axillary involvement; at least 1 of the 1998 St. Gallen high risk criteria; Karnofsky performance status ≥80%; normal organ and bone function; adequate contraception for potentially fertile women • Exclusion: prior systemic therapy or radiotherapy for breast cancer; previous anthracycline or taxane use for any	Intervention arm: 4 x 21-day cycles of FAC followed by 8 weekly cycles of paclitaxel Control arm: 6 x 21-day cycles of FAC

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		malignancy; grade 2+ neurotoxicity; cancer within last 10 years (excluding adequately treated cervical or skin cancer); pregnancy or breastfeeding; HER2+ patients after 2005 (disclosure of adjuvant trastuzumab data)	
Nitz 2014	EC-DOC	• Aged 18-65; T1-3; 1-3 positive lymph nodes; surgery with axillary dissection and clear margins; ECOG performance status <2 • Exclusion: major organ dysfunction; peripheral neuropathy; pregnancy; inflammatory breast cancer	Intervention arm: 4 x 21-day cycles of EC followed by 4 x 21-day cycles of docetaxel Control arm: 6 x 21-day cycles of FEC
Oakman 2013	BIG 02-98	• Women aged 18-70; positive lymph nodes • Exclusion: major comorbidities	Intervention arms: 1) 3 x 21-day cycles of doxorubicin followed by 3 x 21-day cycles of docetaxel followed by 3 cycles of CMF; 2) 4 x 21-day cycles of doxorubicin and docetaxel followed by 3 x 21-day cycles of docetaxel followed by 3 cycles of CMF Control arms: 1) 4 x 21-day cycles of doxorubicin followed by 3 cycles of CMF; 2) 4 x 21-day cycles of doxorubicin and cyclophosphamide followed by 3 cycles of CMF
Polyzos 2010	HORG	• Women aged 18-75; surgery with axillary dissection and clear margins; involved axillary lymph nodes; ECOG performance status 0-2; adequate hematologic, hepatic and cardiac function • Exclusion: pregnancy; cardiac disease contraindicating anthracyclines; previous cancer; other serious morbidities; prior chemotherapy, hormone therapy or radiotherapy	Intervention arm: 4 x 21-day cycles of 100 mg docetaxel followed by 4 x 21-day cycles of EC Control arm: 6 x 21-day cycles of FEC

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Roche 2006	PACS01	• Aged 18-64; surgery with axillary dissection and clear margins; axillary lymph node involvement; WHO performance criteria <2; adequate hematologic, hepatic and cardiac function • Exclusion: pregnancy; cardiac disease contraindicating anthracyclines; previous cancer (except treated skin or cervical cancer); previous radiotherapy, hormone therapy or chemotherapy for breast cancer	Intervention arm: 3 x 21-day cycles of FEC followed by 3 x 21-day cycles of docetaxel Control arm: 6 x 21-day cycles of FEC
Roy 2012	No trial name	• Aged 20-70; Karnofsky performance status ≥70; post-mastectomy; stage II; positive axillary lymph node involvement; normal hematologic and cardiac function • Exclusion: secondary malignancy, co-morbid disease	Intervention arm: 3 x 21-day cycles of AC followed by 3 x 21-day cycles of paclitaxel Control arm: 6 x 21-day cycles of AC
Sakr 2013	No trial name	• Women aged 18-65; ECOG performance status 0-1; surgery with axillary dissection and clear margins; high risk; adequate hematologic, renal, hepatic and cardiac function	Intervention arm: 3 x 21-day cycles of FEC followed by 3 x 21-day cycles of docetaxel Control arm: 6 x 21-day cycles of FEC
Schwentner 2016	ADEBAR	• Women aged 18-70; surgery with axillary dissection and clear margins; ECOG performance status <2; adequate bone marrow; N2-3 • Exclusion: inflammatory breast cancer; concurrent chemotherapy; secondary malignancies; cardiac comorbidities; contraindications to	Intervention arm: 4 x 21-day cycles of EC followed by 4 x 21-day cycles of docetaxel Control arm: 6 x 28-day cycles of FEC

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		study medications; pregnancy	
Vici 2012	GOIM 9902	• Aged 18-70; surgery including axillary dissection; involved axillary lymph nodes; WHO performance status <2; adequate hematologic, hepatic, renal and cardiac function • Exclusion: pregnancy; systemic therapy or radiotherapy; previous cancer; cardiac disease contraindicating anthracyclines; comorbid neuropathy or other severe morbidities	Intervention arm: 4 x 21-day cycles of docetaxel followed by 4 x 21-day cycles of EC Control arm: 4 x 21-day cycles of EC

AC, doxorubicin, cyclophosphamide; AERO, Association Europèenne de Recherche en Oncologie; BCIRG, Breast Cancer International Research Group; CALGB, Cancer and Leukemia Group B; CMF, cyclophosphamide, methotrexate, fluorouracil; DEVA, docetaxel epirubicin adjuvant trial; EC, epirubicin, cyclophosphamide; Ec-Doc, epirubicin docetaxel trial; ECOG, Eastern Cooperative Oncology Groupl; ECTO, European Cooperative Trial in Operable Breast Cancer; EP, epirubicin, paclitaxel; FAC, fluorouracil, doxorubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; GEICAM, Grupo Español de Investigación en Cáncer de Mama; GOIM, Gruppo Oncologico Italia Meridionale; GONO-MIG5, Gruppo Oncologico Nord-Ovest - Mammella Intergruppo Group 5; HER2, human epidermal growth factor receptor 2; HORG, Hellenic Oncology Research Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; RAPP, Risk Assessment and Prevention Program; TAC, docetaxel, doxroubcin, cyclophosphamide; WHO, World Health Organisation

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

Table 3: Summary clinical evidence profile: Comparison 1. EC + docetaxel versus FEC

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC	Corresponding risk: EC + docetaxel			
DFS - All node positive (5 year follow-up)	5yr DFS 78%	5yr DFS 80% (77% to 82%)	HR 0.92 (0.81 to 1.06)	3876 (3 studies)	Moderate[1]
DFS - ER+; node positive (5 year follow-up)	NR	Cannot be calculated	HR 0.52 (0.26 to 1.04)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC	Corresponding risk: EC + docetaxel			
					overall quality
DFS - ER-; node positive (5 year follow-up)	NR	Cannot be calculated	HR 0.49 (0.22 to 1.08)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - HER2+; node positive (5 year follow-up)	5yr DFS 65%	5yr DFS 61% (48% to 71%)	HR 1.16 (0.8 to 1.69)	302 (1 study)	Moderate[2]
DFS - HER2-; node positive (5 year follow-up)	5yr DFS 73%	5yr DFS 72% (65% to 77%)	HR 1.06 (0.83 to 1.35)	949 (1 study)	Moderate[2]
DFS - Triple negative; node positive (5 year follow-up)	5yr DFS 53%	5yr DFS 58% (43% to 70%)	HR 0.87 (0.57 to 1.34)	180 (1 study)	Moderate[2]
OS - All node positive (5 year follow-up)	5yr OS 89%	5yr OS 91% (89% to 93%)	HR 0.81 (0.62 to 1.04)	2512 (2 studies)	Moderate[2]
Treatment-related morbidity – neutropenia (5 year follow-up)	551 per 1000	700 per 1000 (397 to 1000)	RR 1.27 (0.72 to 2.26)	2114 (2 studies)	Very low[3,4]
Treatment-related morbidity - febrile neutropenia (5 year follow-up)	24 per 1000	49 per 1000 (32 to 76)	RR 2.05 (1.33 to 3.17)	2529 (2 studies)	Low[2,5]
Treatment-related morbidity – anaemia (5 year follow-up)	103 per 1000	50 per 1000 (6 to 447)	RR 0.49 (0.06 to 4.35)	2114 (2 studies)	Very low[6,7]
Treatment-related morbidity – thrombocytopenia (5 year follow-up)	154 per 1000	12 per 1000 (8 to 22)	RR 0.08 (0.05 to 0.14)	2114 (2 studies)	Moderate[2]
Treatment-related morbidity –	804 per 1000	716 per 1000 (675 to 764)	RR 0.89 (0.84 to 0.95)	1358 (1 study)	High

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC	Corresponding risk: EC + docetaxel			
leukopenia (5 year follow-up)					
Treatment-related morbidity – nausea (5 year follow-up)	28 per 1000	29 per 1000 (17 to 50)	RR 1.06 (0.62 to 1.8)	2114 (2 studies)	Low[7]
Treatment-related morbidity – vomiting (5 year follow-up)	18 per 1000	35 per 1000 (18 to 70)	RR 1.97 (0.99 to 3.91)	1358 (1 study)	Low[8]
Treatment-related morbidity – diarrhoea (5 year follow-up)	11 per 1000	39 per 1000 (0 to 1000)	RR 3.44 (0.04 to 301.37)	2114 (2 studies)	Very low[7,9]
Treatment-related morbidity – hypersensitivity (5 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 5.43 (0.63 to 46.87)	2114 (2 studies)	Low[7]
Treatment-related morbidity – neurological (5 year follow-up)	1 per 1000	7 per 1000 (1 to 62)	RR 4.93 (0.58 to 42.06)	1358 (1 study)	Low[7]
Treatment-related mortality (5 year follow-up)	5 per 1000	1 per 1000 (0 to 22)	RR 0.2 (0.01 to 4.15)	756 (1 study)	Low[7]
Adequate dose intensity - dose reductions - All cycles	127 per 1000	175 per 1000 (124 to 246)	RR 1.38 (0.98 to 1.94)	756 (1 study)	Low[8]
Adequate dose intensity - dose reductions - 1st half of cycles	33 per 1000	4 per 1000 (1 to 14)	RR 0.13 (0.04 to 0.44)	1364 (1 study)	Moderate[2]
Adequate dose intensity - dose reductions - 2nd half of cycles	95 per 1000	51 per 1000 (34 to 76)	RR 0.54 (0.36 to 0.8)	1364 (1 study)	Moderate[2]
HRQoL - global health (measured by EORTC QLQ-30) (5 year follow-up)		The mean HRQoL - global health (measured by EORTC QLQ-30) in the intervention groups was 3.5 lower		568 (1 study)	Moderate[11]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC	Corresponding risk: EC + docetaxel			
		(7.02 lower to 0.02 higher)			
HRQoL - physical functioning (measured by EORTC QLQ-30) (5 year follow-up)		The mean HRQoL - physical functioning (measured by EORTC QLQ-30) in the intervention groups was 4.3 lower (7.68 to 0.92 lower)		576 (1 study)	Moderate[1] [1]
HRQoL - nausea and vomiting (measured by EORTC QLQ-30) (5 year follow-up)		The mean HRQoL - nausea and vomiting (measured by EORTC QLQ-30) in the intervention groups was 4.3 lower (7.63 to 0.97 lower)		575 (1 study)	Moderate[1] [1]
HRQoL - fatigue (measured by EORTC QLQ-30) (5 year follow-up)		The mean HRQoL - fatigue (measured by EORTC QLQ-30) in the intervention groups was 4.8 higher (0.58 to 9.02 higher)		576 (1 study)	Moderate[1] [1]
HRQoL - systemic therapy side effects (measured by EORTC QLQ-30) (5 year follow-up)		The mean HRQoL - systemic therapy side effects (measured by EORTC QLQ-30) in the intervention groups was 5.5 higher (2.12 to 8.88 higher)		566 (1 study)	Moderate[1] [1]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DFS, disease-free survival; EC: epirubicin, cyclophosphamide; EORTC QLQ-30:

European Organisation for Research and Treatment of Cancer quality of life questionnaire; FEC: fluorouracil, epirubicin, cyclophosphamide; HER2: human epidermal growth factor receptor 2; HR: Hazard ratio; HRQoL: health-related quality of life; NR: not reported; OS: overall survival; RR: Risk ratio;
1 Significant heterogeneity - I2 78%; explored in subsequent subgroup analysis
2 <300 events
3 Significant heterogeneity - I2 98%; cannot explore as data for subgroups of interest not reported
4 95% confidence interval crosses boundary of no effect (1) and both minimally important differences (0.8 and 1.25) based on GRADE default values
5 High attrition in EC-Doc trial
6 Significant heterogeneity - I2 88%; cannot explore as data for subgroups of interest not reported
7 <300 events; 95% confidence interval crosses boundary for no effect (1) and both minimally important differences (0.8 and 1.25) based on GRADE default values
8 <300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important difference (1.25) based on GRADE default values
9 Significant heterogeneity - I2 89%; cannot explore as data for subgroups of interest not reported
10 Significant heterogeneity - I2 90%; explored in subsequent subgroup analysis
11 Risk of detection bias due to subjective, patient-reported outcome

Table 4: Summary clinical evidence profile: Comparison 2. TAC versus FAC

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FAC	Corresponding risk: TAC			
DFS - All node negative (6.4 year follow-up)	6.4yr DFS 82%	6.4yr DFS 86% (82% to 90%)	HR 0.74 (0.55 to 0.98)	1060 (1 study)	Moderate[1]
DFS - T1; node negative (6.4 year follow-up)	NR	Cannot be calculated	HR 0.69 (0.43 to 1.1)	535 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - T2+; node negative (6.4 year follow-up)	NR	Cannot be calculated	HR 0.68 (0.45 to 1.03)	525 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - HER2+; node negative (6.4 year follow-up)	NR	Cannot be calculated	HR 0.73 (0.2 to 2.62)	83 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - HER2-; node negative	NR	Cannot be calculated	HR 0.48 (0.25 to 0.91)	355 (1 study)	Number of events was not

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FAC	Corresponding risk: TAC			
(6.4 year follow-up)					reported - insufficient information to judge imprecision, and therefore overall quality
DFS - Triple negative; node negative (6.4 year follow-up)	NR	Cannot be calculated	HR 0.59 (0.32 to 1.08)	170 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - All node positive (10 year follow-up)	10yr DFS 55%	10yr DFS 62% (67% to 67%)	HR 0.8 (0.68 to 0.94)	1491 (1 study)	High
DFS - HER2+; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.6 (0.43 to 0.83)	319 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall
DFS - HER2-; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.9 (0.74 to 1.1)	1005 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - Triple negative; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.84 (0.56 to 1.25)	192 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FAC	Corresponding risk: TAC			
OS - All node negative (6.4 year follow-up)	6.4yr OS 93%	6.4yr OS 95% (91% to 97%)	HR 0.76 (0.45 to 1.27)	1060 (1 study)	Moderate[1]
OS - All node positive (10 year follow-up)	10yr OS 69%	10yr OS 76% (72% to 80%	HR 0.74 (0.61 to 0.90)	1491 (1 study)	High
OS - HER2+; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.63 (0.43 to 0.93)	319 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - HER2-; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.81 (0.64 to 1.02)	1005 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - Triple negative; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.81 (0.51 to 1.28)	192 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
Treatment-related morbidity – neutropenia (6.4 year follow-up)	803 per 1000	707 per 1000 (667 to 763)	RR 0.88 (0.83 to 0.95)	1051 (1 study)	High
Treatment-related morbidity - febrile neutropenia (6.4 year follow-up)	23 per 1000	96 per 1000 (52 to 178)	RR 4.15 (2.24 to 7.69)	1051 (1 study)	Moderate[1]
Treatment-related morbidity - neutropenic fever (6.4 year follow-up)	27 per 1000	66 per 1000 (36 to 121)	RR 2.44 (1.33 to 4.48)	1051 (1 study)	Moderate[1]
Treatment-related morbidity – anaemia (6.4 year follow-up)	694 per 1000	950 per 1000 (895 to 1000)	RR 1.37 (1.29 to 1.45)	1051 (1 study)	High

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FAC	Corresponding risk: TAC			
Treatment-related morbidity – leukopenia (6.4 year follow-up)	846 per 1000	854 per 1000 (812 to 905)	RR 1.01 (0.96 to 1.07)	1051 (1 study)	High
Treatment-related morbidity – thrombocytopenia (6.4 year follow-up)	50 per 1000	120 per 1000 (78 to 187)	RR 2.4 (1.55 to 3.73)	1051 (1 study)	Moderate[1]
Treatment-related morbidity – nausea (6.4 year follow-up)	746 per 1000	716 per 1000 (664 to 768)	RR 0.96 (0.89 to 1.03)	1051 (1 study)	High
Treatment-related morbidity – vomiting (6.4 year follow-up)	566 per 1000	549 per 1000 (493 to 612)	RR 0.97 (0.87 to 1.08)	1051 (1 study)	High
Treatment-related morbidity – diarrhoea (6.4 year follow-up)	135 per 1000	276 per 1000 (213 to 357)	RR 2.05 (1.58 to 2.65)	1051 (1 study)	Moderate[1]
Treatment-related morbidity - peripheral sensory neuropathy	73 per 1000	131 per 1000 (91 to 190)	RR 1.79 (1.24 to 2.59)	1151 (1 study)	Moderate[1]
Treatment-related morbidity - peripheral motor neuropathy (6.4 year follow-up)	4 per 1000	34 per 1000 (8 to 145)	RR 8.78 (2.05 to 37.65)	1051 (1 study)	Moderate[1]
Treatment-related morbidity – hypersensitivity (6.4 year follow-up)	15 per 1000	43 per 1000 (20 to 96)	RR 2.8 (1.27 to 6.21)	1051 (1 study)	Moderate[1]
Treatment-related morbidity - acute myeloid leukaemia (10.3 year follow-up)	1 per 1000	5 per 1000 (1 to 48)	RR 3.96 (0.44 to 35.32)	1480 (1 study)	Low[2]
Treatment-related morbidity - chronic lymphocytic leukaemia (10.3 year follow-up)	1 per 1000	0 per 1000 (0 to 11)	RR 0.33 (0.01 to 8.08)	1480 (1 study)	Low[2]
Treatment-related morbidity – myelodysplasia (10.3 year follow-up)	1 per 1000	3 per 1000 (0 to 30)	RR 1.98 (0.18 to 21.77)	1480 (1 study)	Low[2]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DFS: disease-free survival; FAC: fluorouracil, doxorubicin, cyclophosphamide; HER2: human epidermal growth factor receptor 2; HR: Hazard ratio; NR: not reported; OS: overall survival; RR: Risk ratio; TAC: docetaxel, doxorubicin, cyclophosphamide
[1] <300 events

[2] *<300 events; 95% confidence interval crosses boundary for no effect (1) and both minimally important differences (0.8 and 1.25) based on GRADE default values*

Table 5: Summary clinical evidence profile: Comparison 3. FEC/FAC + docetaxel/paclitaxel versus FEC/FAC

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC/FAC	Corresponding risk: FEC/FAC + docetaxel/paclitaxel			
DFS - Mixed population: direct evidence (5 to 10 year follow-up)	5yr DFS 74%	5yr DFS 81% (77% to 83%)	HR 0.72 (0.61 to 0.86)	2409 (3 studies)	Moderate[1]
DFS - Mixed population: indirect evidence (comparison) (5 year follow-up)	5yr DFS 74%	5yr DFS 75% (73% to 78%)	HR 0.95 (0.84 to 1.07)	4162 (1 study)	Moderate[2]
DFS - ER+ (5 year follow-up)	NR	Cannot be calculated	HR 1.02 (0.87 to 1.19)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - ER- (5 year follow-up)	NR	Cannot be calculated	HR 0.87 (0.72 to 1.05)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - HER2+ (5 year follow-up)	NR	Cannot be calculated	HR 0.87 (0.69 to 1.09)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - HER2- (5 year follow-up)	NR	Cannot be calculated	HR 1.02 (0.87 to 1.19)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC/FAC	Corresponding risk: FEC/FAC + docetaxel/paclitaxel			
DFS - Node negative (5 year follow-up)	5yr DFS 90%	5yr DFS 92% (90% to 94%)	HR 0.79 (0.62 to 0.99)	1925 (2 studies)	Low[3,4]
DFS - Node positive (5 to 10 year follow-up)	5yr DFS 66%	5yr DFS 68% (66% to 71%)	HR 0.92 (0.84 to 1.01)	3185 (4 studies)	High
DFS - Aged <60 (5 year follow-up)	NR	Cannot be calculated	HR 1 (0.99 to 1.01)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - Aged 60+ (5 year follow-up)	NR	Cannot be calculated	HR 0.9 (0.63 to 1.29)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - T1 (5 year follow-up)	NR	Cannot be calculated	HR 0.87 (0.68 to 1.11)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - T2 (5 year follow-up)	NR	Cannot be calculated	HR 0.97 (0.83 to 1.13)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - T3/4 (5 year follow-up)	NR	Cannot be calculated	HR 0.91 (0.66 to 1.26)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC/FAC	Corresponding risk: FEC/FAC + docetaxel/paclitaxel			
					overall quality
DFS - Triple negative; node positive (8 year follow-up)	NR	Cannot be calculated	HR 0.88 (0.49 to 1.58)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - Mixed population (5 to 10 year follow-up)	5yr OS 85%	5yr OS 86% (85% to 88%)	HR 0.9 (0.8 to 1.01)	6571 (4 studies)	High
OS - Node negative (5 year follow-up)	5yr OS 96%	5yr OS 97% (95% to 98%)	HR 0.79 (0.49 to 1.27)	1925 (1 study)	Low[3,4]
OS - All node positive (8 to 10 year follow-up)	5yr OS 79%	5yr OS 83% (80% to 85%)	HR 0.79 (0.68 to 0.93)	3185 (3 studies)	High
OS - T stage 1; node positive (8 year follow-up)	NR	Cannot be calculated	HR 0.74 (0.44 to 1.24)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - T stage 2+; node positive (8 year follow-up)	NR	Cannot be calculated	HR 0.81 (0.64 to 1.03)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - ER+; node positive (8 year follow-up)	NR	Cannot be calculated	HR 0.79 (0.62 to 1.01)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC/FAC	Corresponding risk: FEC/FAC + docetaxel/paclitaxel			
OS - ER-; node positive (8 year follow-up)	NR	Cannot be calculated	HR 0.72 (0.5 to 1.03)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - HER2+; node positive (8 year follow-up)	NR	Cannot be calculated	HR 0.5 (0.27 to 0.91)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - HER2-; node positive (8 year follow-up)	NR	Cannot be calculated	HR 1.32 (0.98 to 1.76)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
Treatment-related morbidity – neutropenia (5 to 9 year follow-up)	359 per 1000	327 per 1000 (284 to 381)	RR 0.91 (0.79 to 1.06)	10781 (6 studies)	Moderate[5]
Treatment-related morbidity - neutropenia - Direct evidence (5 to 9 year follow-up)	346 per 1000	301 per 1000 (270 to 332)	RR 0.87 (0.78 to 0.96)	6619 (5 studies)	High
Treatment-related morbidity - neutropenia - Indirect evidence (comparison) (5 year follow-up)	382 per 1000	450 per 1000 (420 to 485)	RR 1.18 (1.1 to 1.27)	4162 (1 study)	Moderate[2]
Treatment-related morbidity - febrile neutropenia (5 to 9 year follow-up)	58 per 1000	69 per 1000 (41 to 113)	RR 1.18 (0.71 to 1.94)	8864 (5 studies)	Very low[6,7]
Treatment-related morbidity - febrile neutropenia -	84 per 1000	81 per 1000 (53 to 125)	RR 0.97 (0.63 to 1.5)	4702 (4 studies)	Very low[7,8]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC/FAC	Corresponding risk: FEC/FAC + docetaxel/paclitaxel			
Direct evidence (5 to 9 year follow-up)					
Treatment-related morbidity - febrile neutropenia - Indirect evidence (comparison) (5 year follow-up)	29 per 1000	70 per 1000 (53 to 94)	RR 2.41 (1.8 to 3.23)	4162 (1 study)	Low[2,4]
Treatment-related morbidity – anaemia (5 to 8 year follow-up)	9 per 1000	6 per 1000 (4 to 11)	RR 0.69 (0.4 to 1.2)	6815 (3 studies)	Very low[9,10]
Treatment-related morbidity – thrombocytopenia (5 to 9 year follow-up)	31 per 1000	25 per 1000 (15 to 41)	RR 0.8 (0.49 to 1.3)	7618 (4 studies)	Low[11]
Treatment-related morbidity – leukopenia (5 to 9 year follow-up)	86 per 1000	79 per 1000 (61 to 102)	RR 0.92 (0.71 to 1.18)	2720 (2 studies)	Very low[3,10]
Treatment-related morbidity – lymphopenia (5 year follow-up)	10 per 1000	10 per 1000 (4 to 24)	RR 0.95 (0.39 to 2.34)	1917 (1 study)	Very low[3,11]
Treatment-related morbidity – vomiting (5 to 9 year follow-up)	151 per 1000	135 per 1000 (118 to 153)	RR 0.89 (0.78 to 1.01)	3966 (3 studies)	Moderate[5]
Treatment-related morbidity – nausea (5 to 9 year follow-up)	201 per 1000	191 per 1000 (179 to 205)	RR 0.95 (0.89 to 1.02)	3966 (3 studies)	High
Treatment-related morbidity - nausea/vomiting (5 to 8 year follow-up)	138 per 1000	95 per 1000 (62 to 145)	RR 0.69 (0.45 to 1.05)	6815 (3 studies)	Very low[5,12]
Treatment-related morbidity - nausea/vomiting - Direct evidence (5 to 8 year follow-up)	201 per 1000	113 per 1000 (93 to 135)	RR 0.56 (0.46 to 0.67)	2653 (2 studies)	High
Treatment-related morbidity - nausea/vomiting - Indirect evidence (comparison) (5 year follow-up)	98 per 1000	96 per 1000 (79 to 116)	RR 0.98 (0.81 to 1.18)	4162 (1 study)	Moderate[2]
Treatment-related morbidity – diarrhoea (5 to 9 year follow-up)	32 per 1000	36 per 1000 (23 to 56)	RR 1.12 (0.71 to 1.76)	4965 (2 studies)	Very low[9,11]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC/FAC	Corresponding risk: FEC/FAC + docetaxel/paclitaxel			
Treatment-related morbidity – lethargy (5 to 9 year follow-up)	83 per 1000	107 per 1000 (65 to 177)	RR 1.3 (0.79 to 2.14)	8128 (4 studies)	Very low[7,13]
Treatment-related morbidity - lethargy - Direct evidence (5 to 9 year follow-up)	34 per 1000	36 per 1000 (13 to 97)	RR 1.06 (0.39 to 2.87)	3966 (3 studies)	Very low[3,11,14]
Treatment-related morbidity - lethargy - Indirect evidence (comparison) (5 year follow-up)	130 per 1000	220 per 1000 (191 to 253)	RR 1.69 (1.47 to 1.94)	4162 (1 study)	Moderate[2]
Treatment-related morbidity – neuropathy (5 to 9 year follow-up)	7 per 1000	145 per 1000 (49 to 426)	RR 20.65 (7.02 to 60.74)	8128 (4 studies)	Moderate[15]
Treatment-related morbidity - neuropathy - Direct evidence (5 to 9 year follow-up)	9 per 1000	558 per 1000 (34 to 1000)	RR 63.34 (3.83 to 1048.53)	3966 (3 studies)	Low[16]
Treatment-related morbidity - neuropathy - Indirect evidence (comparison) (5 year follow-up)	5 per 1000	47 per 1000 (25 to 88)	RR 8.98 (4.83 to 16.69)	4162 (1 study)	Low[2,4]
Treatment-related mortality (5 year follow-up)	3 per 1000	3 per 1000 (0 to 62)	RR 1.24 (0.06 to 23.71)	6079 (2 studies)	Very low[3,11,17]
Treatment-related mortality - Direct evidence (5 year follow-up)	7 per 1000	2 per 1000 (0 to 10)	RR 0.3 (0.06 to 1.45)	1917 (1 study)	Very low[3,11]
Treatment-related mortality - Indirect evidence (comparison) (5 year follow-up)	0 per 1000	3 per 1000 (0 to 24)	RR 6.05 (0.73 to 50.18)	4162 (1 study)	Very low[2,11]
Adequate dose intensity - dose reductions - All cycles	36 per 1000	61 per 1000 (41 to 91)	RR 1.68 (1.13 to 2.52)	1999 (1 study)	Moderate[4]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)

CI: Confidence interval; ER: oestrogen receptor; FAC: flouroruacil, doxorubicin, cyclophosphamide; FEC: fluorouracil, epirubicin, cyclophosphamide; HER2: human epidermal growth factor receptor 2; HR: Hazard ratio; NR: not reported; RR: Risk ratio;

[1] Intervention: 32% of Albert 2011 received first 4 cycles of chemotherapy prior to surgery

[2] Control: 39% of control arm received CMF chemotherapy and arms were not otherwise equivalent

[3] *High attrition in GEICAM 2003/02*
[4] *<300 events*
[5] *95% confidence interval crosses boundary for no effect (1) and minimally important difference (0.8) based on GRADE default value*
[6] *Significant heterogeneity - I2 77%; cannot be explored as no data was reported for subgroups of interest*
[7] *95% confidence interval crosses boundary for no effect (1) and both minimally important difference (0.8 and 1.25) based on GRADE default values*
[8] *Significant heterogeneity - I2 77%; cannot be explored as no data was reported for subgroups of interest*
[9] *Control: 39% of control arm in TACT received CMF chemotherapy and arms were not otherwise equivalent*
[10] *<300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important difference (0.8) based on GRADE default value*
[11] *<300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values*
[12] *Significant heterogeneity - I2 89%; explored in subgroup analysis*
[13] *Significant heterogeneity - I2 80%; explored in subgroup analysis*
[14] *Significant heterogeneity - I2 86%; cannot be explored as no data was reported for subgroups of interest*
[15] *Significant heterogeneity - I2 77%; explored in subgroup analysis*
[16] *Significant heterogeneity - I2 83%; cannot be explored as no data was reported for subgroups of interest*
[17] *Significant heterogeneity - I2 80%; cannot be explored as no data was reported for subgroups of interest*

Table 6: Summary clinical evidence profile: Comparison 4. AC/EC + paclitaxel/docetaxel versus AC/EC

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: AC/EC	Corresponding risk: AC/EC + paclitaxel/docetaxel			
DFS - All node positive (2 to 5.8 year follow-up)	2yr DFS 56%	2yr DFS 61% (59% to 64%)	HR 0.84 (0.77 to 0.91)	6980 (4 studies)	High
DFS - T1; node positive (5.3 year follow-up)	NR	Cannot be calculated	HR 1.11 (0.67 to 1.83)	305 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - T2/3; node positive (5.3 year follow-up)	NR	Cannot be calculated	HR 0.95 (0.68 to 1.33)	443 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - ER+; node positive (5.3 year follow-up)	NR	Cannot be calculated	HR 1.14 (0.8 to 1.62)	NR (1 study)	Number of events was not reported - insufficient information to

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: AC/EC	Corresponding risk: AC/EC + paclitaxel/docetaxel			
					judge imprecision, and therefore overall quality
DFS - ER-; node positive (5.3 year follow-up)	NR	Cannot be calculated	HR 0.72 (0.45 to 1.15)	NR (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - HER2+; node positive (5.3 year follow-up)	NR	Cannot be calculated	HR 1.08 (0.57 to 2.05)	94 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - HER2-; node positive (5.3 year follow-up)	NR	Cannot be calculated	HR 1.38 (0.83 to 2.29)	238 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - Mixed population (2 year follow-up)	2yr OS 60%	2yr OS 65% (62% to 68%)	HR 0.85 (0.77 to 0.94)	6280 (2 studies)	High
OS - Node positive (5.3 year follow-up)	5.3yr OS 89%	5.3yr OS 91% (86% to 94%)	HR 0.84 (0.54 to 1.31)	750 (1 study)	Moderate[1]
Treatment-related morbidity – nausea (2 year follow-up)	600 per 1000	762 per 1000 (516 to 1000)	RR 1.27 (0.86 to 1.87)	50 (1 study)	Moderate[2]
Treatment-related morbidity – vomiting (2 year follow-up)	960 per 1000	922 per 1000 (797 to 1000)	RR 0.96 (0.83 to 1.1)	50 (1 study)	Moderate[1]
Treatment-related morbidity - nausea/vomiting (5.3 year follow-up)	59 per 1000	58 per 1000 (32 to 104)	RR 0.98 (0.54 to 1.75)	717 (1 study)	Low[3]
Treatment-related morbidity – diarrhoea (2 to 5.3 year follow-up)	24 per 1000	93 per 1000 (14 to 628)	RR 3.91 (0.58 to 26.45)	767 (2 studies)	Very low[3,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: AC/EC	Corresponding risk: AC/EC + paclitaxel/docetaxel			
Treatment-related morbidity - diarrhoea - AC + paclitaxel vs. AC (2 year follow-up)	320 per 1000	640 per 1000 (336 to 1000)	RR 2 (1.05 to 3.8)	50 (1 study)	Moderate[1]
Treatment-related morbidity - diarrhoea - EC + docetaxel vs. EC 5.3 year follow-up)	3 per 1000	33 per 1000 (4 to 253)	RR 11.7 (1.53 to 89.53)	717 (1 study)	Moderate[1]
Treatment-related morbidity – anaemia (2 to 5.3 year follow-up)	71 per 1000	40 per 1000 (24 to 66)	RR 0.56 (0.34 to 0.92)	767 (2 studies)	Moderate[1]
Treatment-related morbidity – leukopenia (2 year follow-up)	480 per 1000	360 per 1000 (187 to 701)	RR 0.75 (0.39 to 1.46)	50 (1 study)	Low[3]
Treatment-related morbidity – thrombocytopenia (2 to 5.3 year follow-up)	5 per 1000	10 per 1000 (2 to 56)	RR 1.95 (0.36 to 10.58)	767 (2 studies)	Low[3]
Treatment-related morbidity – neurotoxicity (2 to 5.3 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 13.32 (1.75 to 101.15)	767 (2 studies)	Moderate[1]
Treatment-related morbidity – neutropenia 5.3 year follow-up)	542 per 1000	640 per 1000 (569 to 727)	RR 1.18 (1.05 to 1.34)	717 (1 study)	High
Treatment-related morbidity - neutropenic fever 5.3 year follow-up)	28 per 1000	66 per 1000 (32 to 136)	RR 2.34 (1.14 to 4.82)	717 (1 study)	Moderate[1]
Treatment-related morbidity – hypersensitivity 5.3 year follow-up)	3 per 1000	52 per 1000 (7 to 389)	RR 18.53 (2.49 to 137.67)	717 (1 study)	Moderate[1]
Treatment-related mortality (5.4 year follow-up)	20 per 1000	8 per 1000 (2 to 42)	RR 0.42 (0.08 to 2.14)	498 (1 study)	Low[3]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
AC: doxorubicin, cyclophosphamide; CI: Confidence interval; DFS: disease-free survival; EC: epirubicin, cyclophosphamide; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; HR: Hazard ratio; OS: overall survival; RR: Risk ratio
[1] <300 events
[2] 95% confidence interval crosses boundary for no effect (1) and minimally important difference 1.25) based on GRADE default value
[3] <300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values
[4] Significant heterogeneity - I2 71%; explored in subgroup analysis

Table 7: Summary clinical evidence profile: Comparison 5. Epirubicin + docetaxel/paclitaxel versus FEC

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC	Corresponding risk: Epirubicin + docetaxel/paclitaxel			
DFS - Mixed population (10 year follow-up)	10yr DFS 51%	10yr DFS 49% (43% to 55%)	HR 1.05 (0.89 to 1.25)	1055 (1 study)	High
OS - Mixed population (10 year follow-up)	10yr OS 73%	10yr OS 74% (69% to 78%)	HR 0.97 (0.81 to 1.17)	4065 (2 studies)	High
OS - T1/2; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.88 (0.69 to 1.12)	991 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - T3/4; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.87 (0.34 to 2.21)	60 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - Age <60; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.84 (0.63 to 1.12)	735 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - Age 60+; node positive (10 year follow-up)	NR	Cannot be calculated	HR 0.91 (0.62 to 1.33)	320 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
Treatment-related morbidity – anaemia (10 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 2.91 (0.12 to 71.2)	1016 (1 study)	Low[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: FEC	Corresponding risk: Epirubicin + docetaxel/paclitaxel			
Treatment-related morbidity – leukopenia (10 year follow-up)	172 per 1000	177 per 1000 (134 to 230)	RR 1.03 (0.78 to 1.34)	1016 (1 study)	Low[1]
Treatment-related morbidity – neutropenia (10 year follow-up)	30 per 1000	21 per 1000 (10 to 46)	RR 0.71 (0.33 to 1.53)	1016 (1 study)	Low[1]
Treatment-related morbidity - febrile neutropenia (10 year follow-up)	No events	No events	Not estimable	1016 (1 study)	No events so imprecision cannot be determined
Treatment-related morbidity – thrombocytopenia (10 year follow-up)	26 per 1000	8 per 1000 (3 to 24)	RR 0.3 (0.1 to 0.91)	1016 (1 study)	Moderate[2]
Treatment-related morbidity – lymphoma (10 year follow-up)	2 per 1000	1 per 1000 (0 to 16)	RR 0.32 (0.01 to 7.91)	1016 (1 study)	Low[1]
Treatment-related morbidity - acute leukaemia (10 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 2.91 (0.12 to 71.2)	1016 (1 study)	Low[3]
Treatment-related morbidity - nausea/vomiting (10 year follow-up)	78 per 1000	41 per 1000 (24 to 68)	RR 0.52 (0.31 to 0.87)	1016 (1 study)	Moderate[2]
Treatment-related morbidity – diarrhoea (10 year follow-up)	4 per 1000	2 per 1000 (0 to 21)	RR 0.48 (0.04 to 5.33)	1016 (1 study)	Low[1]
Treatment-related morbidity – hypersensitivity (10 year follow-up)	2 per 1000	6 per 1000 (1 to 56)	RR 2.91 (0.3 to 27.85)	1016 (1 study)	Low[1]
Treatment-related morbidity – neurological (10 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 8.72 (0.47 to 161.57)	1016 (1 study)	Low[1]
Adequate dose intensity - dose reductions and/or treatment delays	225 per 1000	175 per 1000 (137 to 225)	RR 0.78 (0.61 to 1)	1055 (1 study)	Moderate[2]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DFS: disease-free survival; FEC: fluorouracil, epirubicin, cyclophosphamide; HR: Hazard ratio; OS: overall survival; RR: Risk ratio
[1] <300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values
[2] <300 events
[3] <300 events; imprecision cannot be determined as no events in either arm

Table 8: Summary clinical evidence profile: Comparison 6. Doxorubicin + docetaxel versus AC

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: AC	Corresponding risk: Doxorubicin + docetaxel			
OS (follow-up not reported)	OS 89% (Follow-up NR)	OS 90% (88% to 91%; Follow-up NR)	HR 0.94 (0.77 to 1.15)	3579 (1 study)	High
Treatment-related morbidity - febrile neutropenia (2 year follow-up)	70 per 1000	405 per 1000 (265 to 620)	RR 5.82 (3.8 to 8.9)	627 (1 study)	Moderate[1]
Treatment-related morbidity - nausea/vomiting (2 year follow-up)	95 per 1000	55 per 1000 (30 to 97)	RR 0.58 (0.32 to 1.02)	627 (1 study)	Low[2]
Treatment-related morbidity – diarrhoea (2 year follow-up)	6 per 1000	29 per 1000 (6 to 133)	RR 4.57 (1 to 20.99)	627 (1 study)	Moderate[1]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
AC: doxorubicin, cyclophosphamidel CI: Confidence interval; HR: Hazard ratio; OS: overall survival; RR: Risk ratio
[1] <300 events
[2] <300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important difference (0.8) based on GRADE default value

Table 9: Summary clinical evidence profile: Comparison 7. Epirubicin + docetaxel versus epirubicin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Epirubicin	Corresponding risk: Epirubicin + docetaxel			
DFS - All node positive (5.4 year follow-up)	5.4yr DFS 71%	5.4yr DFS 79% (74% to 84%)	HR 0.68 (0.51 to 0.9)	803 (1 study)	Moderate[1]
DFS - ER+; node positive (5.4 year follow-up)	NR	Cannot be calculated	HR 0.7 (0.49 to 1)	622 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - ER-; node positive (5.4 year follow-up)	NR	Cannot be calculated	HR 0.61 (0.38 to 0.99)	157 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Epirubicin	Corresponding risk: Epirubicin + docetaxel			
DFS - T1; node positive (5.4 year follow-up)	NR	Cannot be calculated	HR 0.51 (0.31 to 0.84)	356 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - T2; node positive (5.4 year follow-up)	NR	Cannot be calculated	HR 0.76 (0.52 to 1.11)	392 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - T3/4 (5.4 year follow-up)	NR	Cannot be calculated	HR 0.94 (0.36 to 2.45)	51 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
OS - All node positive (5.4 year follow-up)	5.4yr OS 81%	5.4yr OS 87% (82% to 91%)	HR 0.66 (0.46 to 0.94)	803 (1 study)	High
Treatment-related morbidity – anaemia (5.4 year follow-up)	332 per 1000	318 per 1000 (259 to 391)	RR 0.96 (0.78 to 1.18)	773 (1 study)	Moderate[2]
Treatment-related morbidity - acute myeloid leukaemia (5.4 year follow-up)	3 per 1000	1 per 1000 (0 to 21)	RR 0.32 (0.01 to 7.77)	773 (1 study)	Low[3]
Treatment-related morbidity - febrile neutropenia (5.4 year follow-up)	19 per 1000	129 per 1000 (59 to 280)	RR 6.94 (3.19 to 15.09)	773 (1 study)	Moderate[1]
Treatment-related morbidity – leukopenia (5.4 year follow-up)	220 per 1000	251 per 1000 (194 to 324)	RR 1.14 (0.88 to 1.47)	773 (1 study)	Low[5]
Treatment-related morbidity – neutropenia (5.4 year follow-up)	143 per 1000	136 per 1000 (96 to 193)	RR 0.95 (0.67 to 1.35)	773 (1 study)	Low[3]
Treatment-related morbidity – thrombocytopenia (5.4 year follow-up)	8 per 1000	3 per 1000 (0 to 24)	RR 0.32 (0.03 to 3.04)	773 (1 study)	Low[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Epirubicin	Corresponding risk: Epirubicin + docetaxel			
Treatment-related morbidity – diarrhoea (5.4 year follow-up)	56 per 1000	177 per 1000 (111 to 282)	RR 3.17 (1.99 to 5.06)	773 (1 study)	Moderate[1]
Treatment-related morbidity – lethargy (5.4 year follow-up)	40 per 1000	63 per 1000 (34 to 118)	RR 1.59 (0.85 to 2.96)	773 (1 study)	Low[4]
Treatment-related morbidity - nausea/vomiting (5.4 year follow-up)	560 per 1000	453 per 1000 (392 to 521)	RR 0.81 (0.7 to 0.93)	773 (1 study)	High
Treatment-related morbidity - peripheral neuropathy (5.4 year follow-up)	21 per 1000	131 per 1000 (63 to 273)	RR 6.19 (2.98 to 12.85)	773 (1 study)	Moderate[1]
Treatment-related morbidity - unspecified neurological (5.4 year follow-up)	93 per 1000	169 per 1000 (115 to 248)	RR 1.82 (1.24 to 2.67)	773 (1 study)	Moderate[1]
Adequate dose intensity - received 85% of planned dose intensity - Cycles 1-3	919 per 1000	947 per 1000 (910 to 984)	RR 1.03 (0.99 to 1.07)	803 (1 study)	High
Adequate dose intensity - received 85% of planned dose intensity - Cycles 4-6	841 per 1000	757 per 1000 (707 to 816)	RR 0.9 (0.84 to 0.97)	803 (1 study)	High
HRQoL - change in global health status from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in global health status from baseline (as measured by EORTC QoL) in the intervention groups was 0.25 higher (8.46 lower to 8.96 higher)		112 (1 study)	Low[5,6]
HRQoL - change in physical functioning from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in physical functioning from baseline (as measured by EORTC QoL) in the intervention groups was 4.22 lower		114 (1 study)	Very low[5,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Epirubicin	Corresponding risk: Epirubicin + docetaxel			
		(8.36 to 0.08 lower)			
HRQoL - change in role functioning from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in role functioning from baseline (as measured by EORTC QoL) in the intervention groups was 8.39 higher (3.82 lower to 20.6 higher)		114 (1 study)	Very low[5,7]
HRQoL - change in emotional functioning from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in emotional functioning from baseline (as measured by EORTC QoL) in the intervention groups was 4.89 higher (4.04 lower to 13.82 higher)		113 (1 study)	Very low[5,7]
HRQoL - change in cognitive functioning from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in cognitive functioning from baseline (as measured by EORTC QoL) in the intervention groups was 0.93 lower (10.92 lower to 9.06 higher)		113 (1 study)	Low[5,6]
HRQoL - change in social functioning from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in social functioning from baseline (as measured by EORTC QOL) in the intervention groups was 5.56 higher (4.82 lower to 15.94 higher)		112 (1 study)	Low[5,6]
HRQoL - change in fatigue from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in fatigue from baseline (as measured by EORTC QoL) in the intervention		114 (1 study)	Moderate[5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Epirubicin	Corresponding risk: Epirubicin + docetaxel			
		groups was 3.16 lower (11.93 lower to 5.61 higher)			
HRQoL - change in nausea and vomiting from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in nausea and vomiting from baseline (as measured by EORTC QoL) in the intervention groups was 0.76 lower (7.1 lower to 5.58 higher)		114 (1 study)	Moderate[5]
HRQoL - change in diarrhoea from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in diarrhoea from baseline (as measured by EORTC QoL) in the intervention groups was 3.17 higher (5.59 lower to 11.93 higher)		112 (1 study)	Very low[5,7]
HRQoL - change in body image from baseline (as measured by EORTC QoL) (5.4 year follow-up)		The mean HRQoL - change in body image from baseline (as measured by EORTC QoL) in the intervention groups was 0.37 lower (10.32 lower to 9.58 higher)		103 (1 study)	Low[5,6]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)
CI: Confidence interval; DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer; ER: oestrogen receptor; HR: Hazard ratio; HRQoL: health-related quality of life; OS: overall survival; QoL: quality of life; RR: Risk ratio
[1] *<300 events*
[2] *95% confidence interval crosses boundary for no effect (1) and minimally important difference (0.8) based on GRADE default value*
[3] *<300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values*
[4] *<300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important difference (1.25) based on GRADE default value*
[5] *Risk of detection bias as subjective, patient-reported outcome*
[6] *N<400*
[7] *N<400; 95% confidence interval crosses boundary of no effect (0) and minimally important difference based on GRADE default value (0.5xSD)*

Table 10: Summary clinical evidence profile: Comparison 8: Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF versus doxorubicin/epirubicin (± cyclophosphamide) + CMF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: doxorubicin/epirubicin (± cyclophosphamide) + CMF	Corresponding risk: Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF			
DFS - Mixed population (6.3 year follow-up)	NR	Cannot be calculated	HR 0.73 (0.56 to 0.95)	904 (1 study)	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality
DFS - All node positive (3.2 to 8 year follow-up)	3.2yr DFS 65%	3.2yr DFS 68% (65% to 72%)	HR 0.89 (0.78 to 1.01)	3103 (2 studies)	Moderate[1]
DFS - ER+; node positive (8 year follow-up)	8yr DFS 68%	8yr DFS 73% (66% to 78%)	HR 0.82 (0.63 to 1.06)	874 (1 study)	Low[1,2]
DFS - HER2+; node positive (8 year follow-up)	8yr DFS 46%	8yr DFS 64% (41% to 80%)	HR 0.57 (0.29 to 1.14)	106 (1 study)	Low[1,2]
DFS - Triple negative; node positive (8 year follow-up)	8yr DFS 64%	8yr DFS 67% (51% to 79%)	HR 0.90 (0.53 to 1.53)	193 (1 study)	Low[1,2]
OS - Mixed population (follow-up not reported for one trial; 6.3 year follow-up for other trial)	OS 83% (Follow-up NR)	OS 87% (84% to 90%; Follow-up NR)	HR 0.72 (0.57 to 0.93)	1876 (2 studies)	Moderate[2]
OS - All node positive (3.2 to 8 year follow-up)	3.2yr OS 80%	3.2yr OS 82% (79% to 85%)	HR 0.88 (0.75 to 1.04)	3103 (2 studies)	Moderate[1]
Treatment-related morbidity - febrile neutropenia (5 year follow-up)	65 per 1000	140 per 1000 (108 to 182)	RR 2.15 (1.66 to 2.8)	2887 (1 study)	Moderate[1]
Treatment-related morbidity – neutropenia (3.2 year follow-up)	491 per 1000	447 per 1000 (334 to 589)	RR 0.91 (0.68 to 1.2)	216 (1 study)	Low[3]
Treatment-related morbidity – anaemia (3.2 to 5 year follow-up)	46 per 1000	52 per 1000 (9 to 297)	RR 1.14 (0.2 to 6.52)	3103 (2 studies)	Very low[1,4]
Treatment-related morbidity - anaemia - Doxorubicin +	50 per 1000	30 per 1000 (21 to 44)	RR 0.61 (0.42 to 0.89)	2887 (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: doxorubicin/epirubicin (± cyclophosphamide) + CMF	Corresponding risk: Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF			
docetaxel + CMF vs. doxorubicin (+/- cyclophosphamide) + CMF (5 year follow-up)					
Treatment-related morbidity - anaemia - Epirubicin + paclitaxel + CMF vs. epirubicin + cyclophosphamide + CMF (3.2 year follow-up)	9 per 1000	37 per 1000 (4 to 326)	RR 4 (0.45 to 35.21)	216 (1 study)	Low[4]
Treatment-related morbidity – thrombocytopenia (3.2 to 5 year follow-up)	22 per 1000	37 per 1000 (24 to 58)	RR 1.67 (1.07 to 2.62)	3103 (2 studies)	Low[1,2]
Treatment-related morbidity – leukopenia (3.2 year follow-up)	481 per 1000	443 per 1000 (332 to 592)	RR 0.92 (0.69 to 1.23)	216 (1 study)	Low[3]
Treatment-related morbidity – hypersensitivity (5 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 25.74 (1.57 to 422.33)	2887 (1 study)	Low[1,2]
Treatment-related morbidity - nausea/vomiting (3.2 year follow-up)	111 per 1000	64 per 1000 (27 to 159)	RR 0.58 (0.24 to 1.43)	216 (1 study)	Low[5]
Treatment-related morbidity – diarrhoea (5 year follow-up)	10 per 1000	30 per 1000 (15 to 59)	RR 2.93 (1.5 to 5.7)	2887 (1 study)	Low[1,2]
Treatment-related morbidity – neurosensory (3.2 to 5 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 8.78 (1.15 to 67.31)	3103 (2 studies)	Low[1,2]
Treatment-related morbidity – fatigue (3,2 year follow-up)	28 per 1000	74 per 1000 (20 to 272)	RR 2.67 (0.73 to 9.78)	216 (1 study)	Low[4]
Treatment-related mortality (5 year follow-up)	1 per 1000	2 per 1000 (0 to 15)	RR 1.51 (0.16 to 14.53)	2887 (1 study)	Very low[1,4]
Adequate dose intensity - dose reductions	175 per 1000	225 per 1000 (192 to 264)	RR 1.29 (1.1 to 1.51)	2887 (1 study)	Moderate[1]

Rates of DFS and OS in the control group correspond to the trial with the shortest follow-up period (except where number of events are not reported for this trial)

CI: Confidence interval; CMF: cyclophosphamide, methotrexate, flourouracil; DFS: disease-free survival; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; HR: Hazard ratio; OS: overall survival; RR: Risk ratio;
[1] Control: the second control arm in BIG 02-98 included CMF chemotherapy and the arms were not otherwise equivalent
[2] <300 events
[3] <300 events; 95% confidence interval crosses both no effect (1) and minimally important difference (0.8) based on GRADE default value
[4] <300 events; 95% confidence interval crosses both no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values

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 model

An economic analysis was undertaken to estimate the cost-effectiveness of adding taxanes to anthracycline based chemotherapy in the treatment of early and locally advanced breast cancer (see appendix J for the full report of the economic analysis)..

Methods

The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE reference case (see Developing NICE guidelines: the manual). The model considered a 50-year time horizon with future costs and benefits discounted at a rate of 3.5% (as recommended in the NICE reference case).

Clinical data and model approach

The economic analysis was based on overall survival (OS) and disease-free survival (DFS) estimates for each of the treatments included in the analysis. The analysis essentially took the form of a simple partitioned survival analysis, in which 3 mutually exclusive health states were derived from the overall survival and progression-free survival estimates:

- alive without progressed disease
- alive with progressed disease
- dead.

OS and DFS for each of the interventions was estimated using data on absolute and relative risk from the systematic review of the clinical evidence conducted for this topic. Baseline absolute OS and DFS for people receiving anthracycline based chemotherapy were taken from the anthracycline chemotherapy arms in each of the comparisons. OS and DFS estimates for each of the chemotherapy and taxane regimens were estimated by applying the relative treatment effect (using hazard ratios [HRs]) associated with each regimen to the absolute risk estimates.

Mortality from causes other than breast cancer was captured using 2013-2015 life tables for England and Wales from the Office for National Statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. A starting age of 49 years was applied in the model. The other cause mortality estimates were used in conjunction with the OS estimates above to estimate the proportion of people that died of disease-specific and other causes.

Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS and PSS were included. Where possible, all costs were estimated in 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate healthcare resource group (HRG) code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) combined with dosage information from the British National Formulary (BNF). Where costs were not available from eMit, list prices from the BNF were used. Other resource use and cost information was sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the committee.

Chemotherapy delivery costs were sourced from NHS Reference Costs 2015/16 and drug costs were sourced from eMit. Subsequent treatment costs (following disease recurrence or progression) were estimated based on the treatment that would be most likely to be used (based on the estimation of the committee). It was assumed that treatment would vary depending upon the type of recurrence with data from the HERA trial (Cameron 2017) used to estimate the proportion of recurrences that were locoregional (18%), regional (5%), contralateral (8%) and distant (69%).

It was assumed that people with locoregional, regional or contralateral recurrence would undergo a mastectomy if they originally had breast-conserving surgery (42% from Cameron 2017) or a 'major breast procedure' if they originally had a mastectomy (58% from Cameron 2017). It was also assumed that breast reconstruction would be performed (either at the time of mastectomy or delayed). It was further assumed that lymph node clearance would be performed for people with regional recurrence and that radiotherapy would be used if tumours were not previously treated with radiotherapy (24% from Cameron 2017); it was assumed that everyone would receive adjuvant chemotherapy, trastuzumab and peruzumab. It was assumed that with distant recurrence would be treated with chemotherapy, trastuzumab and pertuzumab.

Treatment with trastuzumab is associated with a risk of cardiotoxicity and therefore people receiving trastuzumab typically undergo cardiac monitoring. In clinical practice, echocardiograms are typically used for cardiac monitoring but in some cases multi-gated acquisition (MUGA) scans or cardiac MRI scans may be used. In the model, a weighted average cost per scan was calculated using weightings estimated by the committee. This assumed that 80% of scans would be echocardiograms, 10% would be MUGA scans and 10% would be cardiac MRI scans. The cost for each scan was sourced from NHS reference costs 2015/16. Reflecting clinical practice, it was assumed that people would undergo 5 cardiac monitoring scans in the year that they received trastuzumab.

The cost of post-treatment follow-up to detect disease recurrence was incorporated in the model. It was assumed that people would have clinical follow-up appointments every 3-6 months in years 1 to 3, every 6-12 months in years 4 and 5, and annually thereafter. The cost for each follow-up appointment was estimated to be £120.98 based on the cost of a 'consultant led, non-admitted face to face attendance, follow-up' from NHS Reference Costs 2015/16.

The cost of palliative care was estimated using data from a costing report by the Nuffield Trust (Georghiou 2014). A cost of £7,287 for 3 months was applied, based on the average resource use of people with cancer in the last 3 months of life.

Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality-adjusted life years (QALYs). These are estimated by combining the life year

estimates with utility values or quality of life (QoL) weights associated with being in a particular health state.

The QoL values applied in the model were sourced from Essers 2010, which reported utility values for breast cancer people and was applicable to the UK setting. This study was identified and used by the Evidence Review Group (ERG) in their revised economic analysis as part of the technology appraisal (TA) for pertuzumab in neoadjuvant treatment of HER2-positive breast cancer (NICE TA 424). People in the 'disease-free' health state would have a QoL value of 0.847 which would decrease to 0.810 in people with a recurrence. The QoL value for metastatic disease was applied to people in the last year of life before dying of cancer-specific mortality.

Results

Base-case results

The base-case results of each of the analyses for the overall population and subgroups are shown in Table 11. The results are presented for the average values across all treatment comparisons in each of the subgroups (see appendix J for full results). When interpreting the results of the deterministic analysis, it is important to remember that many of the differences in clinical effectiveness that have been modelled were not statistically significant. There is therefore a lot of uncertainy around the base-case estimates.

The addition of taxanes was found to be cost-effective in most comparisons. In people with node-positive, node-negative, triple negative, HER2-positive and ER-negative disease as well as the overall population, the addition of taxanes was found to be dominant (that is, more effective and less costly). In people with ER-positive disease, the addition of taxanes was found to increase costs and improve effectiveness with a resulting incremental cost-effectiveness ratio (ICER) lower than the NICE threshold of £20,000 per QALY indicating cost-effectiveness. However, the addition of taxanes was not found to be cost-effective in people with HER2-negative disease as the results showed the addition of taxanes to be more costly and more effective but with an ICER above the NICE threshold of £20,000 per QALY.

Table 11: Base-case results

Strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Node-positive					
Chemotherapy	£106,052	-	10.11	-	**-**
Chemotherapy + taxane	£105,032	-£1,020	10.48	*0.37*	**Dominant**
Node-negative					
Chemotherapy	£47,650	-	14.69	-	**-**
Chemotherapy + taxane	£46,156	-£1,494	14.81	*0.12*	**Dominant**
Triplenegative					
Chemotherapy	£101,882	-	9.62	-	**-**
Chemotherapy + taxane	£101,605	-£276	9.90	*0.28*	**Dominant**
HER2-positive					
Chemotherapy	£161,590	-	10.12	-	**-**
Chemotherapy + taxane	£158,424	-£3,166	10.63	*0.51*	**Dominant**
HER2-negative					
Chemotherapy	£66,780	-	10.99	-	**-**

Strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Chemotherapy + taxane	£73,063	£6,283	11.07	*0.09*	**£73,805**
ER-positive					
Chemotherapy	£38,185	-	10.10	-	**-**
Chemotherapy + taxane	£38,232	£47	10.34	*0.24*	**£195**
ER-negative					
Chemotherapy	£32,375	-	11.10	-	**-**
Chemotherapy + taxane	£31,252	-£1,123	11.41	*0.31*	**Dominant**
Overall					
Chemotherapy	£88,986	-	11.98	-	**-**
Chemotherapy + taxane	£87,290	-£1,695	12.18	*0.19*	**Dominant**

Deterministic sensitivity analysis results

A series of deterministic sensitivity analyses was conducted, whereby one input parameter was changed, the model was re-run and the new cost-effectiveness result was recorded. This form of analysis is a useful way of estimating uncertainty and determining the key drivers of the model results.

The results of the deterministic sensitivity analysis are presented in Table 12, showing the ICER result for a comparison between chemotherapy and taxanes versus chemotherapy alone. The results of the analysis are highly sensitive to changes in the HRs for OS and DFS. Indeed, chemotherapy alone is preferred in all comparisons when the upper HR values for OS and DFS are applied. On the other hand, chemotherapy and taxanes are preferred in all comparisons when the lower HR values for OS and DFS are applied.

Table 12: Deterministic sensitivity analysis results

Change made	Node-positive	Node-negative	Triple negative	HER2-positive	HER2-negative	ER-positive	ER-negative	Overall
Base case	**Dominant**	**Dominant**	**Dominant**	**Dominant**	**£73,805**	**£195**	**Dominant**	**Dominant**
Upper HR for mortality	Dominant	£33,303*	£31,749*	£1,017,300	£4,591*	£36,266*	£38,004	£204,952*
Lower HR for mortality	£7,679	Dominant	£12,823	£6,684	£26,901	£6,417	£4,770	£3,573
Upper HR for recurrence	£15,368	£16,065	£97,000	£89,538	£281,923	£49,558	£22,656	£27,840
Lower HR for recurrence	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
Upper HR for mortality	Dominant	£8,810*	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated

Change made	Node-positive	Node-negative	Triple negative	HER2-positive	HER2-negative	ER-positive	ER-negative	Overall
and recurrence								
Lower HR for mortality and recurrence	Dominant	Dominant	Dominant	Dominant	£3,789	Dominant	Dominant	Dominant
Baseline OS = 80%	Dominant	Dominant	Dominant	Dominant	£60,419	£9,950	£2,503	Dominant
Baseline OS = 70%	£2,964	Dominant	£3,504	Dominant	£62,678	£14,180	£6,693	£6,415
Baseline DFS = 80%	£2,223	Dominant	£4,174	£12,507	£73,024	£3,830	£2,074	Dominant
Baseline DFS = 70%	Dominant	Dominant	£2,610	£5,636	£82,533	£948	Dominant	Dominant6
Treatment effect duration = 10 years	Dominant	Dominant	Dominant	Dominant	£124,093	Dominant	Dominant	Dominant
Treatment effect duration = 20 years	Dominant	Dominant	Dominant	Dominant	£99,851	Dominant	Dominant	Dominant
Lifetime treatment effect duration	Dominant	Dominant	Dominant	Dominant	£94,164	Dominant	Dominant	Dominant
Reduced G-CSF cost	Dominant	Dominant	Dominant	Dominant	£71,105	Dominant	Dominant	Dominant
Consistent regimens only	Dominant	Dominant	Dominant	Dominant	Dominated	£13,788	£1,972	£664

** ICER results show a scenario where the addition of taxanes was found to be less effective and less expensive. Therefore, interpretation of the ICER result changes with values above £20,000 per QALY indicating cost-effectiveness.*

Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base-case were replaced with values drawn from distributions around the mean values.

In all the subgroups it can be seen that, as the threshold increases, the probability of chemotherapy being cost-effective decreases while the probability of chemotherapy and

taxane being cost-effective increases. However, while the pattern is very similar in all comparisons the probability of chemotherapy and taxanes being cost-effective at the threshold of £20,000 per QALY used by NICE varies significantly. In the node-positive, node-negative, triple-negative, HER2-positive, ER-positive, ER-negative subgroups and the overall population it can be seen that chemotherapy and taxanes have the highest probability of being cost-effective at a threshold of £20,000 per QALY (probabilities of 100%, 98%, 77%, 88%, 90%, 99% and 99%, respectively). In the HER2-negative population, chemotherapy alone had the highest probability of being cost-effective at a threshold of £20,000 per QALY (86%).

In all the subgroups it was found thatas the threshold increases, the probability of chemotherapy being cost-effective decreases while the probability of chemotherapy and taxane being cost-effective increases. However, while the pattern is very similar in all comparisons the probability of chemotherapy and taxanes being cost-effective at the threshold of £20,000 per QALY used by NICE varies significantly. In the node-positive, node-negative, triple-negative, HER2-positive, ER-positive and ER-negative subgroups as well as the overall population, chemotherapy and taxanes have the highest probability of being cost-effective at a threshold of £20,000 per QALY (probabilities of 100%, 98%, 77%, 88%, 90%, 99% and 99%, respectively). In the HER2-negative population, chemotherapy alone had the highest probability of being cost-effective at a threshold of £20,000 per QALY (86%).

Conclusion

It is difficult to draw any firm conclusion around cost-effectiveness in this area as the clinical evidence upon which it is based is too uncertain. In particular, there is a lack of high quality clinical evidence showing clear differences between the approaches. However, it does appear that in most scenarios where taxanes were assumed to improve overall and disease-free survival, their use would be cost-effective. Furthermore, the evidence is variable for the different subgroups with a greater degree of certainty around some of the higher risk subgroups such as people with node-positive disease.

Formal consensus

Due to the lack of available subgroup evidence for elderly people and those with cardiac disease identified by the literature review, the committee agreed that a modified form of the nominal group technique would be the most appropriate method for producing recommendations regarding the appropriateness of adding taxanes to anthracycline-based chemotherapy regimens for this population; the committee agreed it was important to make receommendations in this area due to current uncertainty and lack of available treatment options for these groups. The method used for the nominal group technique is described in full within the methods chapter.

Key issues related to taxane use among elderly people and those with cardiac disease were identified from relevant papers identified by the current search results, key papers and guidelines identified by the committee and additional hand-searching, and from protocol discussions with the committee. These were used to generate statements covering the elderly and cardiac disease groups. These statements were placed into a questionnaire and distributed to the committee present (14 out of 16 members) to be rated. However, a large proportion of the committee members felt they had insufficient knowledge in this area to provide a rating. Therefore, consensus agreement was based on ratings from a subset of the committee who had expert knowledge in this area (primarily oncologists and a pharmacist; 1 statement was rated by 4 members, 4 statements were rated by 5 members, 3 statements were rated by 6 members; 2 statements were rated by 7 members, and 1 statement was rated by 8 members). Percentage agreement values were calculated and comments were collated for each statement; the rankings and comments were then presented to the committee to facilitate a structured discussion. One statement was redrafted based on the

comments from the committee members and redistributed for rating; this round was completed by 14 committee members.

A brief summary of level of consensus is depicted in Table 13 below. A blank copy of the questionnaire (including re-rated statements) can be found in appendix M and consensus ratings can be found in appendix N.

Table 13: Summary of nominal group technique process followed for the development of recommendation on adding taxanes to anthracycline-based chemotherapy regimens for elderly people and for those with cardiac disease

Round 1		Round 2		Number of recommendations generated
Level of consensus	Statements N (total = 11)	Level of consensus	Statements N (total = 1)	1
High (≥80%)	4	High (≥80%)	1	
Moderate (60-80%)	2	Moderate (60-80%)	0	
Low (<60%)	5	Low (<60%)	0	

Evidence statements

Comparison 1. EC + docetaxel versus FEC

Critical outcomes

Overall survival

- There is moderate quality evidence from 2 RCTs (N=2,512) that there is no clinically important effect of docetaxel on overall survival at 5 year follow-up for people with node positive invasive breast cancer.

Disease-free survival

- There is moderate quality evidence from 3 RCTs (N=3,876) that there is no clinically important effect of docetaxel on disease-free survival at 5 year follow-up for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of docetaxel on disease-free survival at 5 year follow-up for people with ER+, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of docetaxel on disease-free survival at 5 year follow-up for people with ER-, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is moderate quality evidence from 1 RCT (N=302) that there is no clinically important effect of docetaxel on disease-free survival at 5 year follow-up for people with HER2+, node positive invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=949) that there is no clinically important effect of docetaxel on disease-free survival at 5 year follow-up for people with HER2-, node positive invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=180) that there is no clinically important effect of docetaxel on disease-free survival at 5 year follow-up for people with triple negative, node positive invasive breast cancer.

Treatment-related morbidity

- There is very low quality evidence from 2 RCTs (N=2,114) that EC + docetaxel produced clinically meaningful increases in neutropenia at 5 year follow-up compared with FEC for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 2 RCTs (N=2,529) that EC + docetaxel produced clinically meaningful increases in febrile neutropenia at 5 year follow-up compared with FEC for people with invasive breast cancer.
- There is very low quality evidence from 2 RCTs (N=2,114) that EC + docetaxel produced clinically meaningful reductions in anaemia at 5 year follow-up compared with FEC for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 2 RCTs (N=2,114) that EC + docetaxel produced clinically meaningful reductions in thrombocytopenia at 5 year follow-up compared with FEC for people with invasive breast cancer.
- There is high quality evidence from 1 RCT (N=1,358) that there is no clinically important effect of docetaxel on leukopenia at 5 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 2 RCTs (N=2,114) that there is no clinically important effect of docetaxel on nausea at 5 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1,358) that EC + docetaxel produced clinically meaningful increases in vomiting at 5 year follow-up compared with FEC for people with invasive breast cancer; however, the effect was not statistically significant.
- There is very low quality evidence from 2 RCTs (N=2,114) that EC + docetaxel produced clinically meaningful increases in diarrhoea at 5 year follow-up compared with FEC for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 2 RCTs (N=2,114) that EC + docetaxel produced clinically meaningful increases in hypersensitivity at 5 year follow-up compared with FEC for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=1,358) that EC + docetaxel produced clinically meaningful increases in neurological side effects at 5 year follow-up compared with FEC for people with invasive breast cancer; however, the effect was not statistically significant.

Important outcomes

Adequate dose intensity

- There is low quality evidence from 1 RCT (N=756) that EC + docetaxel produced clinically meaningful increases in number of people with dose reductions (across all cycles) compared with FEC for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=1,364) that EC + docetaxel produced clinically meaningful reductions in number of people with dose reductions during the first half of chemotherapy cycles compared with FEC for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1,364) that EC + docetaxel produced clinically meaningful reductions in number of people with dose reductions during the second half of chemotherapy cycles compared with FEC for people with invasive breast cancer.

Treatment-related mortality

- There is low quality evidence from 1 RCT (N=756) that EC + docetaxel produced clinically meaningful reductions in treatment-related mortality at 5 year follow-up compared with FEC for people with invasive breast cancer; however, the effect was not statistically significant.

Health-related quality of life

- There is moderate quality evidence from 1 RCT (N=568) that there is no clinically important difference in global health-related quality of life at 5 year follow-up between EC + docetaxel and FEC chemotherapy for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=576) that there is no clinically important difference in physical functioning at 5 year follow-up between EC + docetaxel and FEC chemotherapy for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=575) that there is no clinically important difference in nausea and vomiting (measured by EORTC QLQ-30) at 5 year follow-up between EC + docetaxel and FEC chemotherapy for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=576) that there is no clinically important difference in fatigue (measured by EORTC QLQ-30) at 5 year follow-up between EC + docetaxel and FEC chemotherapy for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=566) that there is no clinically important difference in systemic side effects (measured by EORTC QLQ-30) at 5 year follow-up between EC + docetaxel and FEC chemotherapy for people with invasive breast cancer.

Comparison 2. TAC versus FAC

Critical outcomes

Overall survival

- There is moderate quality evidence from 1 RCT (N=1,060) that there is no clinically important effect of docetaxel on overall survival at 6.4 year follow-up for people with node negative invasive breast cancer.
- There is high quality evidence from 1 RCT (N=1,491) that TAC produced clinically meaningful increases in overall survival at 10 year follow-up compared with FAC for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=319) that TAC produced clinically meaningful increases in overall survival at 10 year follow-up compared with FAC for people with HER2+, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=1,005) that there is no clinically important effect of docetaxel on overall survival at 10 year follow-up for people with HER2-, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=192) that there is no clinically important effect of docetaxel on overall survival at 10 year follow-up for people with triple negative, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Disease-free survival

- There is moderate quality evidence from 1 RCT (N=1,060) that TAC produced clinically meaningful increases in disease-free survival at 6.4 year follow-up compared with FAC for people with node negative invasive breast cancer.
- There is evidence from 1 RCT (N=535) that there is no clinically important effect of docetaxel on disease-free survival at 6.4 year follow-up for people with T stage 1, node negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

- There is evidence from 1 RCT (N=525) that there is no clinically important effect of docetaxel on disease-free survival at 6.4 year follow-up for people with T stage 2+, node negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=83) that there is no clinically important effect of docetaxel on disease-free survival at 6.4 year follow-up for people with HER2+, node negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=355) that TAC produced clinically meaningful increases in disease-free survival at 6.4 year follow-up compared with FAC for people with HER2-, node negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=170) that there is no clinically important effect of docetaxel on disease-free survival at 6.4 year follow-up for people with triple negative, node negative invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is high quality evidence from 1 RCT (N=1,491) that TAC produced clinically meaningful increases in disease-free survival 10 year follow-up compared with FAC for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=319) that TAC produced clinically meaningful increases in disease-free survival at 10 year follow-up compared with FAC for people with HER2+, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=1,005) that there is no clinically important effect of docetaxel on disease-free survival at 10 year follow-up for people with HER2-, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=192) that there is no clinically important effect of docetaxel on disease-free survival at 10 year follow-up for people with triple negative, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Treatment-related morbidity

- There is high quality evidence from 1 RCT (N=1,051) that there is no clinically important effect of TAC on neutropenia at 6.4 year follow-up compared with FAC for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1,051) that TAC produced clinically meaningful increases in febrile neutropenia at 6.4 year follow-up compared with FAC for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1,051) that TAC produced clinically meaningful increases in neutropenic fever at 6.4 year follow-up compared with FAC for people with invasive breast cancer.
- There is high quality evidence from 1 RCT (N=1,051) that TAC produced clinically meaningful increases in anaemia at 6.4 year follow-up compared with FAC for people with invasive breast cancer.
- There is high quality evidence from 1 RCT (N=1,051) that there is no clinically important effect of docetaxel on leukopenia at 6.4 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1,051) that TAC produced clinically meaningful increases in thrombocytopenia at 6.4 year follow-up compared with FAC for people with invasive breast cancer.

- There is high quality evidence from 1 RCT (N=1,051) that there is no clinically important effect of docetaxel on nausea at 6.4 year follow-up for people with invasive breast cancer.
- There is high quality evidence from 1 RCT (N=1,051) that there is no clinically important effect of docetaxel on vomiting at 6.4 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1,051) that TAC produced clinically meaningful increases in diarrhoea at 6.4 year follow-up compared with FAC for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1,151) that TAC produced clinically meaningful increases in peripheral sensory neuropathy at 6.4 year follow-up compared with FAC for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1,051) that TAC produced clinically meaningful increases in peripheral motor neuropathy at 6.4 year follow-up compared with FAC for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1,051) that TAC produced clinically meaningful increases in hypersensitivity c at 6.4 year follow-up compared with FAC for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1,480) that TAC produced clinically meaningful increases in acute myeloid leukaemia at 10.3 year follow-up compared with FAC for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=1,480) that TAC produced clinically meaningful reductions in chronic lymphocytic leukaemia at 10.3 year follow-up compared with FAC for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=1,480) that TAC produced clinically meaningful increases in myelodysplasia at 10.3 year follow-up compared with FAC for people with invasive breast cancer; however, the effect was not statistically significant.

Important outcomes

Adequate dose intensity

- No evidence was found for this outcome.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 3. FEC/FAC + docetaxel/paclitaxel versus FEC/FAC

Critical outcomes

Overall survival

- There is high quality evidence from 4 RCTs (N=6,571) that there is no clinically important effect of taxane addition on overall survival at 5 to 10 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1,925) that there is no clinically important effect of taxane addition on overall survival at 5 year follow-up for people with node negative invasive breast cancer.

- There is high quality evidence from 3 RCTs (N=3,185) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful increases in overall survival at 8 to 10 year follow-up for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on overall survival at 8 year follow-up for people with T stage 1, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on overall survival at 8 year follow-up for people with T stage 2+, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on overall survival at 8 year follow-up for people with ER+, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on overall survival at 8 year follow-up for people with ER-, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful increases in overall survival at 8 year follow-up for people with HER2+, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on overall survival at 8 year follow-up for people with HER2-, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Disease-free survival

- There is moderate quality evidence from 3 RCTs (N=2,409) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful increases in disease-free survival at 5 to 10 year follow-up for people with invasive breast cancer (based on direct evidence).
- There is moderate quality evidence from 1 RCT (N=4,162) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people with invasive breast cancer (based on indirect evidence).
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people with ER+ invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people with ER- invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people with HER2+ invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people with HER2- invasive breast

cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

- There is low quality evidence from 2 RCTs (N=1,925) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful increases in disease-free survival at 5 year follow-up for people with node negative invasive breast cancer.
- There is high quality evidence from 4 RCTs (N=3,185) that there is no clinically important effect of taxane addition on disease-free survival at 5 to 10 year follow-up for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people aged <60 years with invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people aged ≥60 years with invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people with T stage 1 invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people with T stage 2 invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5 year follow-up for people with T stage 3/4 invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 8 year follow-up for people with triple negative, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Treatment-related morbidity

- There is moderate quality evidence from 6 RCTs (N=10,781) that there is no clinically important effect of taxane addition on neutropenia at 5 to 9 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 4 RCTs (N=4,702) that there is no clinically important effect of taxane addition on febrile neutropenia at 5 to 9 year follow-up for people with invasive breast cancer (based on direct evidence).
- There is low quality evidence from 1 RCT (N=4,162) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful increases in febrile neutropenia at 5 year follow-up for people with invasive breast cancer (based on indirect evidence).
- There is very low quality evidence from 3 RCTs (N=6,815) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful reductions in anaemia at 5 to 8 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 4 RCTs (N=7,618) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful reductions in thrombocytopenia at 5 to 9 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.

- There is very low quality evidence from 2 RCTs (N=2,720) that there is no clinically important effect of taxane addition on leukopenia at 5 to 9 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=1,917) that there is no clinically important effect of taxane addition on lymphopenia at 5 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 3 RCTs (N=3,966) that there is no clinically important effect of taxane addition on vomiting at 5 to 9 year follow-up for people with invasive breast cancer.
- There is high quality evidence from 3 RCTs (N=3,966) that there is no clinically important effect of taxane addition on nausea at 5 to 9 year follow-up for people with invasive breast cancer.
- There is high quality evidence from 2 RCTs (N=2,653) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful reductions in nausea and vomiting (combined outcome) for people with invasive breast cancer (based on direct evidence).
- There is moderate quality evidence from 1 RCT (N=4,162) that there is no clinically important effect of taxane addition on nausea and vomiting (combined outcome) at 5 year follow-up for people with invasive breast cancer (based on indirect evidence).
- There is very low quality evidence from 2 RCTs (N=4,965) that there is no clinically important effect of taxane addition on diarrhoea at 5 to 9 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 3 RCTs (N=3,966) that there is no clinically important effect of taxane addition on lethargy at 5 to 9 year follow-up for people with invasive breast cancer (based on direct evidence).
- There is moderate quality evidence from 1 RCT (N=4,162) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful increases in lethargy at 5 year follow-up for people with invasive breast cancer (based on indirect evidence).
- There is moderate quality evidence from 4 RCTs (N=8,128) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful increases in neuropathy at 5 to 9 year follow-up for people with invasive breast cancer.

Important outcomes

Adequate dose intensity

- There is moderate quality evidence from 1 RCT (N=1999) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful increases in the number of people with dose reductions for people with invasive breast cancer.

Treatment-related mortality

- There is very low quality evidence from 1 RCT (N=1,917) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful reductions in treatment-related mortality at 5 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant (based on direct evidence).
- There is very low quality evidence from 1 RCT (N=4,162) that the addition of taxanes to FEC or FAC chemotherapy produced clinically meaningful increases in treatment-related mortality at 5 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant (based on indirect evidence).

Health-related quality of life

- No evidence was found for this outcome.

Comparison 4. AC/EC + paclitaxel/docetaxel versus AC/EC

Critical outcomes

Overall survival

- There is high quality evidence from 2 RCTs (N=6,280) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful increases in overall survival at 2 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=750) that there is no clinically important effect of taxane addition on overall survival at 5.3 year follow-up for people with node positive invasive breast cancer.

Disease-free survival

- There is high quality evidence from 4 RCTs (N=6,980) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful increases in disease-free survival at 2 to 5.8 year follow-up for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=305) that there is no clinically important effect of taxane addition on disease-free survival at 5.3 year follow-up for people with T stage 1, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=443) that there is no clinically important effect of taxane addition on disease-free survival at 5.3 year follow-up for people with T stage 2 or 3, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5.3 year follow-up for people with ER+, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=NR) that there is no clinically important effect of taxane addition on disease-free survival at 5.3 year follow-up for people with ER-, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=94) that there is no clinically important effect of taxane addition on disease-free survival at 5.3 year follow-up for people with HER2+, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=238) that there is no clinically important effect of taxane addition on disease-free survival at 5.3 year follow-up for people with HER2-, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Treatment-related morbidity

- There is moderate quality evidence from 1 RCT (N=50) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful increases in nausea at 2 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=50) that there is no clinically important effect of taxane addition on vomiting at 2 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=717) that there is no clinically important effect of taxane addition on nausea and vomiting (combined outcome) at 5.3 year follow-up for people with invasive breast cancer.

- There is very low quality evidence from 2 RCTs (N=767) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful increases in diarrhoea at 2 to 5.3 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=50) that the addition of paclitaxel to AC chemotherapy produced clinically meaningful increases in diarrhoea at 2 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=717) that the addition of docetaxel to EC chemotherapy produced clinically meaningful increases in diarrhoea at 5.3 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 2 RCTs (N=767) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful reductions in anaemia at 2 to 5.3 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=50) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful reductions in leukopenia at 2 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 2 RCTs (N=767) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful increases in thrombocytopenia at 2 to 5.3 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=767) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful increases in unspecified neurotoxicity at 5.3 year follow-up for people with invasive breast cancer.
- There is high quality evidence from 1 RCT (N=717) that there is no clinically important effect of taxane addition on neutropenia at 5.3 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=717) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful increases in neutropenic fever at 5.3 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=717) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful increases in hypersensitivity at 5.3 year follow-up for people with invasive breast cancer.

Important outcomes

Adequate dose intensity

- No evidence was found for this outcome.

Treatment-related mortality

- There is low quality evidence from 1 RCT (N=717) that the addition of taxanes to AC or EC chemotherapy produced clinically meaningful reductions in treatment-related mortality at 5.4 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 5. Epirubicin + docetaxel/paclitaxel versus FEC

Critical outcomes

Overall survival

- There is high quality evidence from 2 RCTs (N=4,065) that there is no clinically important difference in overall survival at 10 year follow-up for epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy for people with invasive breast cancer.
- There is evidence from 1 RCT (N=991) that there is no clinically important difference in overall survival at 10 year follow-up for epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy for people with T stage 1 or 2, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=60) that there is no clinically important difference in overall survival at 10 year follow-up for epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy for people with T stage 3 or 4, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=735) that there is no clinically important difference in overall survival at 10 year follow-up for epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy for people aged <60 years with node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=320) that there is no clinically important difference in overall survival at 10 year follow-up for epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy for people aged ≥60 years with node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Disease-free survival

- There is high quality evidence from 1 RCT (N=1,055) that there is no clinically important difference in disease-free survival at 10 year follow-up for epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy for people with invasive breast cancer.

Treatment-related morbidity

- There is low quality evidence from 1 RCT (N=1,016) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful increases in anaemia at 10 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=1,016) that there is no clinically important difference in leukopenia at 10 year follow-up for epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1,016) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful reductions in neutropenia at 10 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=1,016) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful reductions in thrombocytopenia at 10 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1,016) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful reductions in

lymphoma at 10 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.

- There is low quality evidence from 1 RCT (N=1,016) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful increases in acute leukaemia at 10 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=1,016) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful reductions in nausea and vomiting (combined outcome) at 10 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1,016) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful reductions in diarrhoea at 10 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=1,016) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful increases in hypersensitivity at 10 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=1,016) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful increases in unspecified neurological side effects at 10 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.

Important outcomes

Adequate dose intensity

- There is moderate quality evidence from 1 RCT (N=1,055) that epirubicin + docetaxel or paclitaxel compared with FEC chemotherapy produced clinically meaningful reductions in the number of people with dose reductions and/or treatment delays for people with invasive breast cancer.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 6. Doxorubicin + docetaxel versus AC

Critical outcomes

Overall survival

- There is high quality evidence from 1 RCT (N=3,579) that there is no clinically important difference in overall survival (follow-up NR) for doxorubicin + docetaxel compared with AC chemotherapy for people with invasive breast cancer.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related morbidity

- There is moderate quality evidence from 1 RCT (N=627) that doxorubicin + docetaxel compared with AC chemotherapy produced clinically meaningful increases in febrile neutropenia at 2 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=627) that doxorubicin + docetaxel compared with AC chemotherapy produced clinically meaningful reductions in nausea and vomiting (combined outcome) at 2 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=627) that doxorubicin + docetaxel compared with AC chemotherapy produced clinically meaningful increases in diarrhoea at 2 year follow-up for people with invasive breast cancer.

Important outcomes

Adequate dose intensity

- No evidence was found for this outcome.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 7. Epirubicin + docetaxel versus epirubicin

Critical outcomes

Overall survival

- There is high quality evidence from 1 RCT (N=803) that the addition of docetaxel produced clinically meaningful increases in overall survival at 5.4 year follow-up for people with node positive invasive breast cancer.

Disease-free survival

- There is moderate quality evidence from 1 RCT (N=803) that the addition of docetaxel produced clinically meaningful increases in disease-free survival at 5.4 year follow-up for people with node positive invasive breast cancer.
- There is evidence from 1 RCT (N=622) that the addition of docetaxel produced clinically meaningful increases in disease-free survival at 5.4 year follow-up for people with ER+, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=157) that the addition of docetaxel produced clinically meaningful increases in disease-free survival at 5.4 year follow-up for people with ER-, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=356) that the addition of docetaxel produced clinically meaningful increases in disease-free survival at 5.4 year follow-up for people with T stage 1, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is evidence from 1 RCT (N=392) that there is no clinically important effect of the addition of docetaxel on disease-free survival at 5.4 year follow-up for people with T stage 2, node positive invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

- There is evidence from 1 RCT (N=51) that there is no clinically important effect of the addition of docetaxel on disease-free survival at 5.4 year follow-up for people with T stage 3 or 4, invasive breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

Treatment-related morbidity

- There is moderate quality evidence from 1 RCT (N=773) that there is no clinically important effect of the addition of docetaxel on anaemia at 5.4 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=773) that the addition of docetaxel produced clinically meaningful reductions in acute myeloid leukaemia at 5.4 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=773) that the addition of docetaxel produced clinically meaningful increases in febrile neutropenia at 5.4 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=773) that there is no clinically important effect of the addition of docetaxel on leukopenia at 5.4 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=773) that there is no clinically important effect of the addition of docetaxel on neutropenia at 5.4 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=773) that the addition of docetaxel produced clinically meaningful reductions in thrombocytopenia at 5.4 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=773) that the addition of docetaxel produced clinically meaningful increases in diarrhoea at 5.4 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=773) that the addition of docetaxel produced clinically meaningful increases in lethargy at 5.4 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is high quality evidence from 1 RCT (N=773) that there is no clinically important effect of the addition of docetaxel on nausea and vomiting (combined outcome) at 5.4 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=773) that the addition of docetaxel produced clinically meaningful increases in peripheral neuropathy at 5.4 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=773) that the addition of docetaxel produced clinically meaningful increases in unspecified neurological side effects at 5.4 year follow-up for people with invasive breast cancer.

Important outcomes

Adequate dose intensity

- There is high quality evidence from 1 RCT (N=803) that there is no clinically meaningful effect of the addition of docetaxel on the number of individuals with invasive breast cancer receiving at least 85% of planned chemotherapy dose during the first three cycles.
- There is high quality evidence from 1 RCT (N=803) that there is no clinically meaningful effect of the addition of docetaxel on the number of individuals with invasive breast cancer receiving at least 85% of planned chemotherapy dose during the final three cycles.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- There is low quality evidence from 1 RCT (N=112) that there is no clinically meaningful effect of the addition of docetaxel on global health-related quality of life at 5.4 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=114) that there is no clinically meaningful effect of the addition of docetaxel on physical functioning at 5.4 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=114) that there is no clinically meaningful effect of the addition of docetaxel on role functioning at 5.4 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=113) that there is no clinically meaningful effect of the addition of docetaxel on emotional functioning at 5.4 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=113) that there is no clinically meaningful effect of the addition of docetaxel on cognitive functioning at 5.4 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=112) that there is no clinically meaningful effect of the addition of docetaxel on social functioning at 5.4 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=114) that there is no clinically meaningful effect of the addition of docetaxel on fatigue (measured by EORTC QLQ-30) at 5.4 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=114) that there is no clinically meaningful effect of the addition of docetaxel on nausea and vomiting (measured by EORTC QLQ-30) at 5.4 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=112) that there is no clinically meaningful effect of the addition of docetaxel on diarrhoea (measured by EORTC QLQ-30) at 5.4 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=103) that there is no clinically meaningful effect of the addition of docetaxel on body image at 5.4 year follow-up for people with invasive breast cancer.

Comparison 8. Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF versus doxorubicin/epirubicin (± cyclophosphamide) + CMF

Critical outcomes

Overall survival

- There is moderate quality evidence from 2 RCTs (N=1,876) that the addition of taxanes produced clinically meaningful increases in overall survival at 6.3 year follow-up for people with invasive breast cancer.
- There is moderate quality evidence from 2 RCTs (N=3,103) that there is no clinically important effect of the addition of taxanes on overall survival at 3.2 to 8 year follow-up for people with node positive invasive breast cancer.

Disease-free survival

- There is evidence from 1 RCT (N=904) that the addition of taxanes produced clinically meaningful increases in disease-free survival at 6.3 year follow-up for people with invasive

breast cancer. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.

- There is moderate quality evidence from 2 RCTs (N=3,103) that there is no clinically important effect of the addition of taxanes on disease-free survival at 3.2 to 8 year follow-up for people with node positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=874) that there is no clinically important effect of the addition of taxanes on disease-free survival at 8 year follow-up for people with ER+, node positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=106) that there is no clinically important effect of the addition of taxanes on disease-free survival at 8 year follow-up for people with HER2+, node positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=193) that there is no clinically important effect of the addition of taxanes on disease-free survival at 8 year follow-up for people with triple negative, node positive invasive breast cancer.

Treatment-related morbidity

- There is moderate quality evidence from 1 RCT (N=2,887) that the addition of taxanes produced clinically meaningful increases in febrile neutropenia at 5 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=216) that there is no clinically important effect of the addition of taxanes on neutropenia at 3.2 year follow-up for people with invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=2,887) that the addition of docetaxel produced clinically meaningful reductions in anaemia at 5 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=216) that the addition of paclitaxel produced clinically meaningful increases in anaemia at 3.2 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 2 RCTs (N=3,103) that the addition of taxanes produced clinically meaningful increases in thrombocytopenia at 3.2 to 5 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=216) that there is no clinically important effect of the addition of taxanes on leukopenia at 3.2 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=2,887) that the addition of taxanes produced clinically meaningful increases in hypersensitivity at 5 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=216) that the addition of taxanes produced clinically meaningful reductions in nausea and vomiting (combined outcome) at 3.2 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=2,887) that the addition of taxanes produced clinically meaningful increases in diarrhoea at 5 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 2 RCTs (N=3,103) that the addition of taxanes produced clinically meaningful increases in unspecified neurosensory side effects at 3.2 to 5 year follow-up for people with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=216) that the addition of taxanes produced clinically meaningful increases in fatigue at 3.2 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.

Important outcomes

Adequate dose intensity

- There is moderate quality evidence from 1 RCT (N=2,887) that the addition of taxanes produced clinically meaningful increases in the number of individuals with dose reductions for people with invasive breast cancer.

Treatment-related mortality

- There is very low quality evidence from 1 RCT (N=2,887) that the addition of taxanes produced clinically meaningful increases in treatment-related mortality at 5 year follow-up for people with invasive breast cancer; however, the effect was not statistically significant.

Health-related quality of life

- No evidence was found for this outcome.

Economic evidence statement

- There is evidence from a de novo cost-utility analysis that the addition of taxanes to chemotherapy was cost-effective in people with node-positive, node-negative, triple negative, HER2-positive, ER-negative and ER-positive breast cancer as well as the overall 'mixed' population with breast cancer. The analysis was directly applicable with minor limitations.

Recommendations

E1. For people with breast cancer of sufficient risk that chemotherapy is indicated, offer a regimen that contains both a taxane[a] and anthracycline[b].

E3. Discuss with people the benefits and risks of adding a taxane to anthracycline-containing regimens. Topics to discuss include:

- the benefits of reduced cardiac toxicity and reduced nausea
- the risks of additional side-effects, including neuropathy, neutropenia and hypersensitivity
- the different adverse effects and dosing frequencies of different docetaxel and paclitaxel regimens, and the additional clinic visits that may be needed
- that absolute benefit is proportional to absolute risk of recurrence.

E4. Weekly and fortnightly paclitaxel should be available locally because these regimens are tolerated better than 3-weekly docetaxel, particularly in people with comorbidities.

Rationale and impact

Why the committee made the recommendations

There was good evidence of improved survival when taxanes are added to anthracycline-based chemotherapy in people with node-positive and node-negative breast cancer. In both groups, the benefits and risks of treatment should be discussed because of the potential side effects associated with taxanes. Three-weekly docetaxel was identified as a regimen with potentially more toxicity than weekly or fortnightly paclitaxel.

a Please refer to the Summary of Product Characteristics for individual taxanes because there are differences in their licensed indications.

b Please refer to the Summary of Product Characteristics for individual anthracyclines because there are differences in their licensed indications.

Impact of the recommendations on practice

These recommendations may result in a substantial change in practice because of increased taxane use, particularly for people with node-negative breast cancer and comorbidities.

In addition, there will be an increase in weekly and fortnightly chemotherapy regimens being offered (for people who cannot tolerate 3-weekly regimens). These regimens have a higher cost because they are more resource intensive, and may affect capacity in chemotherapy services.

The committee's discussion of the evidence

Interpreting the evidence

This review was concerned with determining if there are survival benefits associated with the addition of taxanes to anthracycline-based chemotherapy and therefore overall survival and disease-free survival were prioritised as critical outcomes. Treatment-related morbidity was also selected as a critical outcome due to the additional toxicities associated with taxanes.

Adequate dose-intensity was selected as an important outcome as potential toxicities may lead to dose-reductions, which could in turn affect the effectiveness of the chemotherapy regimen. Treatment-related mortality was considered an important outcome due to the seriousness of potential side effects of both taxanes (for example, neutropenia) and anthracyclines (for example, cardiac toxicity). Finally, health-related quality of life evidence was considered important as it may be impacted by treatment-related morbidity and different chemotherapy schedules, such as those administered in weekly compared with three-weekly cycles.

The quality of the evidence

The quality of the evidence was assessed using GRADE. For the outcomes of overall and disease-free survival the majority of the evidence was moderate to high quality. The main reason evidence was downgraded was due to imprecision around the estimate due to a small number of events of interest and wide confidence intervals. The evidence was further downgraded to low quality for some of subgroups of interest due to high attrition in some trials. Further, it was not possible to judge the quality of evidence for a number of the subgroups as the numbers of people and/or events of interest were not reported in some papers, and so it was not possible to determine the imprecision around the estimates and, therefore, the overall quality.

The recommendations for use in node-positive and node-negative disease were based on moderate to high quality evidence of improved overall and disease-free survival associated with the addition of taxanes to anthracycline-based chemotherapy regimens. A strong ('offer') recommendation was made for people with both node-positive and node positive breast cancer. The most consistent benefit was observed in people with node-positive disease and although there was less consistent evidence of a benefit in the lower risk node-negative group, there will be some individuals with sufficiently high risk of recurrence to benefit from taxanes.

The treatment-related morbidity evidence was of mixed quality (very low to high) but the majority was of moderate quality; the main reason evidence was downgraded was due to imprecision around the estimate. This evidence formed the basis for recommendation E3.

The treatment-related mortality evidence was low and very low quality due to imprecision around the estimate as there were very few events of interest and the results were inconsistent.

The adequate-dose intensity evidence was mainly of moderate or high quality but the evidence was inconsistent; therefore, the committee did not think any firm conclusion could be reached regarding the likelihood of anthracycline dose reductions following taxane and anthracycline containing chemotherapy regimens compared with non-taxane containing regimens.

The health-related quality of life evidence ranged from very low to moderate quality. All of the evidence was downgraded for risk of detection bias due to the subjective nature of this outcome as there was no blinding in the trials; some of the evidence was further downgraded due to imprecision around the estimate. There was no difference between the intervention and control arms for health-related quality of life for any of the outcomes examined.

Although there were high levels of agreement for statements which informed and supported recommendations, the formal consensus method, used for generating recommendations about elderly populations and those with cardiac disease, constitutes low quality evidence.

Benefits and harms

The main benefits associated with the addition of taxanes to anthracycline-based chemotherapy were improved survival and a potential reduction in cardiotoxicity. Specifically, there was evidence of a 4-5% and 4-7% overall survival improvement associated with the addition of taxanes in mixed and node-positive populations, respectively. There was evidence of a 7%, 7-8% and 2-4% disease-free survival improvement associated with the addition of taxanes in mixed, node-positive, and node-negative populations, respectively. A potential reduction in cardiotoxicity was concluded from formal consensus involving the oncologists and pharmacist committee members; therefore, the committee agrred that taxane-containing regimens should be used with those with comorbidities to reduce cardiac risk which may affect ability to cope with comorbidities. A specific recommendation was not made for elderly populations as the committee agreed that physical health and functioning needed considering in addition to age.

The benefits need to be balanced against potential harms. The main harms associated with the addition of taxanes to anthracycline-based chemotherapy are increased neutropenia, neuropathy, diarrhoea and hypersensitivity to taxanes. Specifically rates of neutropenia ranged from 3-33% higher, neuropathy ranged from 3-21% higher, diarrhoea ranged from 2-15% higher, and hypersensitivity to taxanes ranged from 1-5% higher following the addition of taxanes to anthracycline-based chemotherapy regimens.

The committee agreed that survival benefits are normally prioritised by people ahead of other outcomes; further, there was no consistent evidence of a detrimental effect of taxanes on treatment-related mortality or health-related quality of life. Therefore, the potential benefits were thought to outweigh the potential harms. However, the committee made a recommendation to discuss the benefits and harms with individual patients, including that the absolute benefit is proportional to the absolute risk, to help patients make an informed decision about taxane treatment.

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. An economic analysis was undertaken for this question assessing the cost-effectiveness of the addition of taxanes to anthracycline based chemotherapy regimens in various subgroups.

The addition of taxanes was found to be cost-effective in most comparisons. In people with node-positive, node-negative, triple negative, HER2-positive and ER-negative disease as well as the overall population, the addition of taxanes was found to be dominant (that is, more effective and less costly). In people with ER-positive disease, the addition of taxanes was found to increase costs and improve effectiveness with a resulting incremental cost-

effectiveness ratio (ICER) lower than the NICE threshold of £20,000 per QALY indicating cost-effectiveness. However, the addition of taxanes was not found to be cost-effective in patients with HER2-negative disease, with an ICER above the NICE threshold of £20,000 per QALY.

While these results were of some interest, the committee was aware of the high degree of uncertainty around the clinical inputs upon which the analysis was based. This was reflected somewhat in the sensitivity analysis, in which the conclusion of the analysis was shown to change when using the upper HR value for overall and disease-free survival. However, the analysis did show that in most scenarios where taxanes were assumed to improve overall and disease-free survival their use was cost-effective. Furthermore, the evidence was variable for the different subgroups with a higher degree of certainty around some of the higher risk subgroups such as node-positive patients.

Additional resources will be required to implement these recommendations as there will be an increase in the number of people receiving taxanes, particularly weekly and fortnightly regimens. Capacity of chemotherapy centres will need to be increased in order to deliver the additional sessions required.

Other factors the committee took into account

The committee was aware that the side-effect profile associated with 3-weekly docetaxel is worse than that associated with weekly or fortnightly paclitaxel, and this was confirmed by the formal consensus ratings; the committee agreed that 3-weekly docetaxel is not appropriate for elderly patients, but that there should not be age restrictions associated with weekly paclitaxel use. The guideline evidence review did not compare different taxane regimens against each other; however, the most consistent evidence of increased neutropenia and hypersensitivity in the evidence review came from comparisons of anthracycline- and docetaxel-based chemotherapy regimens compared with anthracycline-based chemotherapy regimens (for example, EC plus docetaxel versus FEC, TAC versus FAC, doxorubicin plus docetaxel versus AC, and epirubicin plus docetaxel versus epirubicin alone). Further, when looking at the mixed comparisons, greatest evidence of increased neutropenia came from TACT, PACS 01, Sakr 2013, BIG 02-98 and GOIM 9902 which all used docetaxel in addition to anthracyclines. In contrast, evidence from GEICAM 9906 and AER0-B2000, which used paclitaxel in addition to anthracyclines, showed either no difference in side effects between arms, or reduced side effects in the intervention taxane-containing arm. Three-weekly docetaxel is, therefore, not considered appropriate for people with serious comorbidities.

Weekly or fortnightly paclitaxel is not currently available in all centres. Therefore people with comorbidities may not receive taxane treatment if weekly or fortnightly paclitaxel is not available. The committee has recommended that weekly or fortnightly paclitaxel should be available locally to overcome this inequality. However, the committee noted that weekly paclitaxel (and to a lesser extent fortnightly paclitaxel) is more disruptive to the patient due to the number of scheduled treatment sessions, so there may be an impact on health-related quality of life, and some patients (such as those who travel long distances for treatment or are working) may choose to receive a three-weekly regimen.

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Appendices

Appendix A – Review protocols

Review protocol for 5.1. Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline- based adjuvant chemotherapy?

Field (based on PRISMA-P)	Content
Review question	Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?
Type of review question	Intervention review
Objective of the review	The objective of this review is to determine the benefit of taxanes in addition to anthracycline based on stage and phenotype of breast cancer. Recommendations will aim to cover what groups should be offered taxane containing chemotherapy regimens.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive early or locally advanced breast cancer who have undergone breast surgery and are suitable for anthracycline based adjuvant chemotherapy
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Taxane (docetaxel and paclitaxel) containing regimen
Eligibility criteria – comparator(s)/control or reference (gold) standard	Non-taxane containing regimen
Outcomes and prioritisation	Critical (up to 3 outcomes) • Overall survival (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference) • Treatment-related morbidity (MID: GRADE default values) Important but not critical • Adequate dose intensity (MID: GRADE default values) • Treatment-related mortality (MID: any statistically significant difference)

Field (based on PRISMA-P)	Content
	• HRQoL/patient satisfaction (MID: values from the literature where available; otherwise GRADE default values) 10 year follow-up periods 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 • WHOQOL-100: 1 point
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs • Modified nominal group technique will be used to make recommendations regarding appropriateness of offering taxanes to individuals with comorbidities if there is not suffiicent subgroup data to make recommendations.
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): • T stage • Nodal status (positive, negative) • Receptor status ○ Triple negative ○ HER2+ ○ ER+ • Performance status (Karnofsky grade 80-100/ECOG grade 0-1; Karnofsky grade 60-80/ECOG grade 2; Karnofsky grade 10-50/ECOG grade 3-4) • Cardiovascular disease (absent/present) • Age (<60, ≥60)
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

Field (based on PRISMA-P)	Content
	reviewer. Dual sifting will not be performed for this review 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. The current review question is broader than that covered by the previous guideline and technology appraisals. Therefore, the search will be undertaken from 1985, as the first phase 1 trials on the use of taxanes in breast cancer were published in the mid-late 1980s. 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 topics: TA108: Paclitaxel for the adjuvant treatment of early node-positive breast cancer & TA109: Docetaxel for the adjuvant treatment of early node-positive breast cancer Date of TA108: 27/09/2006 Date of TA109: 26/09/2006 Date of update search from previous guideline: 24/07/2008 Relevant recommendation(s) from previous guidelines: TA108) Paclitaxel is not recommended as an option for the adjuvant treatment of women with early node-positive breast cancer. TA109) Docetaxel (given with doxorubicin and cyclophosphamide) is recommended as a possible adjuvant treatment for women with early node-positive breast cancer. CG80 1) Offer docetaxel to patients with lymph node-positive breast cancer patients as part of an adjuvant chemotherapy regimen.CG80 2) Do not offer paclitaxel as an adjuvant treatment for lymph node-positive breast cancer.
Author contacts	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.

Field (based on PRISMA-P)	Content
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.

Field (based on PRISMA-P)	Content
PROSPERO registration number	N/A

BCS, breast cancer subscale; ECOG, Eastern Cooperative Oncology Group; 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 receptor 2; HRQoL, health-related quality of life; 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

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 September 20**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 25 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

#	Searches
29	Paget's Disease, Mammary/ use prmz
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	exp Paclitaxel/ use prmz
34	paclitaxel/ use oemezd
35	docetaxel/ use oemezd
36	(docetaxel$ or taxotere$).tw.
37	(nsc-125973 or nsc125973).tw.
38	("Abi 007" or Abi007).tw.
39	(Bms 181339 or Bms181339).tw.
40	(paclitax$ or taxol or anzatax$ or onxol$ or paxen$ or praxel$ or abraxan$ or coroxan$ or genexol$ or hunxol$ or intaxel$ or paxceed$ or yewtaxan$).tw.
41	taxane$.tw.
42	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43	Adjuvant Chemotherapy/ use prmz
44	adjuvant therapy/ use oemezd
45	(postoperat$ or post-operat$ or post operat$ or postsurg$ or post-surg$ or post surg$).tw.
46	(adjuvant$ or adjunct or auxiliary).tw.
47	((after or follow$) adj (surg$ or operat$)).tw.
48	(concurrent$ or sequential$ or polychemotherap$).tw.
49	43 or 44 or 45 or 46 or 47 or 48
50	32 and 42 and 49
51	limit 50 to yr="2006 -Current"
52	remove duplicates from 51
53	Limit 60 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

2 Date of last search: 25 September 2017

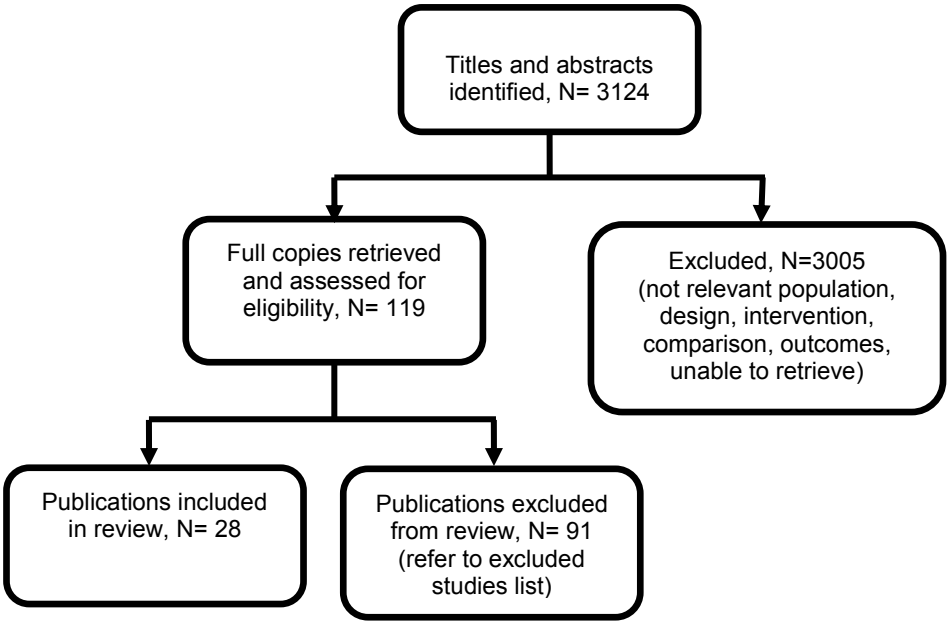
#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [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: [Paclitaxel] explode all trees
#23	(docetaxel* or taxotere*):ti,ab,kw (Word variations have been searched)
#24	("Abi 007" or Abi007):ti,ab,kw (Word variations have been searched)
#25	(paclitax* or taxol or anzatax* or onxol* or paxen* or praxel* or abraxan* or coroxan* or genexol* or hunxol* or intaxel* or paxceed* or yewtaxan*):ti,ab,kw (Word variations have been searched)
#26	#22 or #23 or #24 or #25
#27	#21 and #26 Publication Year from 2006 to 2017

1

Appendix C – Clinical evidence study selection

Figure 1: Flow diagram of clinical article selection for addition of taxanes to anthracycline-based chemotherapy



Appendix D – Clinical evidence tables

2 **Table 14: Evidence table for adjuvant chemotherapy**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Coudert, B., Asselain, B., Campone, M., Spielmann, M., Machiels, J. P., Penault-Llorca, F., Serin, D., Levy, C., Romieu, G., Canon, J. L., Orfeuvre, H., Piot, G., Petit, T., Jerusalem, G., Audhuy, B., Veyret, C., Beauduin, M., Eymard, J. C., Martin, A. L., Roche, H., Extended benefit from sequential administration of docetaxel after standard fluorouracil, epirubicin, and cyclophosphamide regimen for node-positive breast cancer: The 8-Year Follow-Up results of the UNICANCER-PACS01 Trial, Oncologist, 17, 900-909, 2012 **Ref Id** 552134 **Country/ies where the study was carried out** France and Belgium **Study type** RCT **Aim of the study**	**Sample size** 1,999 **Characteristics** Gender: 100% female Age: NR Ethnicity: NR **Inclusion criteria** Women aged 18 to 64 with node positive unilateral breast cancer; undergone surgery with clear margins and axillary dissection; WHO performance status <2; adequate renal, hepatic and cardiac function. **Exclusion criteria** History of cardiac disease that contraindicated anthracycline use **Reported subgroups**	**Interventions** **Intervention arm:** 3 cycles of FEC100 followed by 3 cycles of docetaxel **Control arm:** 6 cycles of FEC100	**Details** **Intervention arm (taxane + anthracycline):** within 42 days of surgery patients commenced 3 21-day cycles of FEC100 - 500 mg/m2 fluorouracil, 100 mg/m2 epirubicin and 500 mg/m2 cyclophosphamide on day 1. This was followed by 3 21-day of 100 mg/m2 docetaxel administered on day 1. Following chemotherapy, hormone-receptor positive patients received 5 years of tamoxifen; for hormone-receptor negative patients, tamoxifen was given according to physician discretion for post-menopausal patients and prohibited for pre-menopausal patients. Radiotherapy was mandated within 4 weeks of the final chemotherapy cycle for those that had breast conserving surgery. **Control arm (antracycline only):** within 42 days of surgery patients commenced 6 21-day cycles of FEC100 - 500 mg/m2 fluorouracil, 100 mg/m2 epirubicin and 500 mg/m2 cyclophosphamide on day 1. Following chemotherapy, hormone-receptor positive patients received 5 years of	**Results** **Whole sample (node positive, cardiac disease absent):** **OS (8 year follow-up):** O-E: -28.38; V: 98.66 **DFS (8 year follow-up):** O-E: -26.90; V: 165.55 **Adequate dose intensity - dose reductions:** taxane + anthracycline 61/1003; anthracycline only 36/996 **T stage 1 (node positive, cardiac disease absent):** **OS (8 year follow-up):** O-E: -4.38; V: 14.54 **T stage 2+ (node positive, cardiac disease absent):** **OS (8 year follow-up):** O-E: -14.30; V: 67.86 **ER+ (node positive, cardiac disease absent):**	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** 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** 97% of control arm completed 6 cycles and 96.1% of intervention arm: Low **Selective reporting**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To evaluate the survival benefit of docetaxel after FEC chemotherapy at 8 year follow-up **Study dates** Enrolled June 1997 to March 2000 **Source of funding** Ligue Nationale Contre le Cancer and Sanofi-Aventis	All node positive and cardiac disease absent; T1; T2+; ER+/-; HER2+/-		tamoxifen; for hormone-receptor negative patients, tamoxifen was given according to physician discretion for post-menopausal patients and prohibited for pre-menopausal patients. Radiotherapy was mandated within 4 weeks of the final chemotherapy cycle for those that had breast conserving surgery.	**OS (8 year follow-up):** O-E: -14.61; V: 62 **ER- (node positive, cardiac disease absent):** **OS (8 year follow-up):** O-E: -9.93; V: 30.23 **HER2+ (node positive, cardiac disease absent):** **OS (8 year follow-up):** O-E: -7.35; V: 10.60 **HER2- (node positive, cardiac disease absent):** **OS (8 year follow-up):** O-E: -12.45; V: 45.38	Low **Indirectness** None **Limitations** **Other information** PACS01 trial
Full citation Martin, M., Segui, M. A., Anton, A., Ruiz, A., Ramos, M., Adrover, E., Aranda, I., Rodriguez-Lescure, A., Grosse, R., Calvo, L., Barnadas, A., Isla, D., Martinez Del Prado, P., Borrego, M. R., Zaluski, J., Arcusa, A., Munoz, M., Lopez Vega, J. M., Mel, J. R., Munarriz, B., Llorca, C., Jara, C., Alba, E., Florian, J., Li, J., Lopez Garcia-Asenjo, J. A., Saez, A., Rios, M. J., Almenar, S., Peiro,	**Sample size** 1,060 **Characteristics** Gender: 100% female Age: taxane + anthracycline median 50; anthracycline only median 49; range 23-74 Ethnicity: NR	**Interventions** **Intervention arm:** six cycles of TAC (docetaxel, doxorubicin and cyclophosphamide) **Control arm:** six cycles of FAC (fluorouracil, doxorubicin and cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** patients received 6 21-day cycles of TAC: on day 1 patients received 75 mg/m2 docetaxel, 50 mg/m2 doxorubicin and 500 mg/m2 cyclophosphamide. Dexamethasone and ciprofloxacin were given to prevent oedema and infection; the protocol was amended to include G-CSF for all patients in this arm due to >25%	**Results** **Whole sample (node negative):** **DFS (median follow-up 77 months):** O-E: -14.43; V: 37.42 **OS (median follow-up 77 months):** O-E: -3.98; V: 14.49 **Treatment-related morbidities -**	**Selection bias: random sequence generation** Stratified blocks: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
G., Lluch, A., Adjuvant docetaxel for high-risk, node-negative breast cancer, New England Journal of Medicine, 363, 2200-2210, 2010 **Ref Id** 615482 **Country/ies where the study was carried out** Spain, Germany and Poland **Study type** RCT **Aim of the study** To determine the value of taxanes for node-negative breast cancer **Study dates** Randomised June 1999 to March 2004 **Source of funding** Sanofi-Aventis	**Inclusion criteria** Women aged 18-70; negative axillary lymph nodes (at least 10 examined); meet at least 1 of the 1998 St. Gallen high risk criteria (tumour size >2cm, ER- and PR-, grade 2 or 3, aged <35 years); within 60 days of surgery **Exclusion criteria** No additional criteria reported **Reported subgroups** All node negative; T1; T2+; HER2+; HER2-; triple negative		incidence of neutropenic fever. 20 mg tamoxifen was given daily for 5 years to people with hormone-positive tumours; radiotherapy was mandatory for all patients who had breast-conserving surgery and was given following mastectomy for tumours >5cm according to local protocols. **Control arm (anthracycline only):** patients received 6 21-day cycles of FAC: on day 1 patients received 500 mg/m2 fluorouracil, 50 mg/m2 doxorubicin and 500 mg/m2 cyclophosphamide. Any patients that had an episode of febrile neutropenia or infection were given prophylactic antibiotics and G-CSF for all remaining cycles. 20 mg tamoxifen was given daily for 5 years to people with hormone-positive tumours; radiotherapy was mandatory for all patients who had breast-conserving surgery and was given following mastectomy for tumours >5cm according to local protocols.	**neutropenia:** taxane + anthracycline: 378/532; anthracycline only 417/519 **Treatment-related morbidities - febrile neutropenia:** taxane + anthracycline: 51/532; anthracycline only 12/519 **Treatment-related morbidities - neutropenic fever:** taxane + anthracycline: 35/532; anthracycline only 14/519 **Treatment-related morbidities - anaemia:** taxane + anthracycline: 504/532; anthracycline only 360/519 **Treatment-related morbidities - leukopenia:** taxane + anthracycline: 456/532; anthracycline only 439/519 **Treatment-related morbidities - thrombocyctopenia:** taxane + anthracycline: 64/532; anthracycline only 26/519 **Treatment-related morbidities - nausea:** taxane + anthracycline: 379/532; anthracycline only 387/519	Unclear **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** 11 patients in the intervention arm and 2 patients in the control arm did not receive protocol assigned treatment; 95% and 98% of patients completed 6 cycles of treatment in the intervention and control arms, respectively: Low **Selective reporting** Low **Indirectness** None **Limitations** Limited number of deaths occurred to date; therefore longer follow-up is needed

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Treatment-related morbidities - vomiting: taxane + anthracycline: 292/532; anthracycline only 294/519 **Treatment-related morbidities - diarrhoea:** taxane + anthracycline: 147/532; anthracycline only 70/519 **Treatment-related morbidities - peripheral sensory neuropathy:** taxane + anthracycline: 83/532; anthracycline only 38/519 **Treatment-related morbidities - peripheral motor neuropathy:** taxane + anthracycline: 18/532; anthracycline only 2/519 **Treatment-related morbidities - hypersensitivity:** taxane + anthracycline: 23/532; anthracycline only 8/519 **T1 (node negative):** **DFS (median follow-up 77 months):** O-E: -6.46; V: 17.42 **T2+ (node negative):**	**Other information** GEICAM 9805 trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				DFS (median follow-up 77 months): O-E: -8.44; V: 21.90 **HER2+ (node negative):** **DFS (median follow-up 77 months):** O-E: -0.74; V: 2.34 **HER2- (node negative):** **DFS (median follow-up 77 months):** O-E: -6.91; V: 9.36 **Triple-negative (node negative):** **DFS (median follow-up 77 months):** O-E: -5.56; V: 10.55	
Full citation Sakr, H., Hamed, R. H., Anter, A. H., Yossef, T., Sequential docetaxel as adjuvant chemotherapy for node-positive or/and T3 or T4 breast cancer: clinical outcome (Mansoura University), Medical oncology (Northwood, London, England), 30, 457, 2013 **Ref Id**	**Sample size** 657 **Characteristics** Gender: 100% female Age: taxane + anthracycline median 45; anthracycline only median 47; range 24-69 Ethnicity: NR	**Interventions** **Intervention arm:** 3 cycles of FEC (fluorouracil, epirubicin + cyclophosphamide) + 3 cycles of docetaxel **Control arm:** 6 cycles of FEC (fluorouracil, epirubicin + cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** patients received 3 21-day cycles of FEC (500 mg/m2 IV fluorouracil, 100 mg/m2 IV epirubicin and 500 mg/m2 IV cyclophosphamide given on day 1) followed by 3 21-day cycles of 100 mg/m2 IV docetaxel. Patients received prophylactic corticosteroids (6 doses starting 12 hours before docetaxel infusion and ending	**Results** **DFS (5 year follow-up):** O-E: -15.54; V: 39.13 **OS (5 year follow-up):** O-E: -18.03; V: 57.28 **Treatment-related morbidity - neutropenia:** taxane + anthracycline 71/330; anthracycline only 82/327	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
552601 **Country/ies where the study was carried out** Egypt **Study type** RCT **Aim of the study** To determine the efficacy of adding docetaxel to an FEC chemotherapy regimen for people with node positive or T3/4 breast cancer **Study dates** January 2006 to January 2010 **Source of funding** No sources reported	**Inclusion criteria** Women aged 18-65; ECOG performance status 0-1; surgical resection (including axillary dissection) with clear margins; high risk (node positive and/or T3/4); adequate hematologic, renal, hepatic, and cardiac function **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest		18 hours after). Radiotherapy began within 4 weeks of chemotherapy and was mandated in those that received breast-conserving surgery - radiotherapy to the chest wall and supraclavicular nodes was recommended following mastectomy. 20 mg tamoxifen daily was given for 5 years after chemotherapy. **Control arm (anthracycline only):** patients received 6 21-day cycles of FEC (500 mg/m2 IV fluorouracil, 100 mg/m2 IV epirubicin and 500 mg/m2 IV cyclophosphamide given on day 1). Radiotherapy began within 4 weeks of chemotherapy and was mandated in those that received breast-conserving surgery - radiotherapy to the chest wall and supraclavicular nodes was recommended following mastectomy. 20 mg tamoxifen daily was given for 5 years after chemotherapy.	**Treatment-related morbidity - febrile neutropenia:** taxane + anthracycline 27/330; anthracycline only 22/327 **Treatment-related morbidity - anaemia:** taxane + anthracycline 2/330; anthracycline only 4/327 **Treatment-related morbidity - thrombocytopenia :** taxane + anthracycline 2/330; anthracycline only 2/327 **Treatment-related morbidity - nausea/vomiting:** taxane + anthracycline 37/330; anthracycline only 62/327	Unclear **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** 97% of intervention arm and 96% of control arm received 6 cycles of treatment: Low **Selective reporting** Low **Indirectness** None **Limitations** **Other information**
Full citation Mackey, J. R., Martin, M., Pienkowski, T., Rolski, J., Guastalla, J. P., Sami, A., Glaspy, J., Juhos, E., Wardley, A., Fornander, T., Hainsworth, J.,	**Sample size** 1,491 **Characteristics** Gender: 100% female	**Interventions** **Intervention arm:** FAC (fluorouracil, doxorubicin and cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** patients received 6 21-day cycles of TAC: on the first day of each cycle they received 50 mg/m2 doxorubicin (15 minute IV	**Results** **Whole sample (node positive):** **DFS (10 year follow-up):** O-E: - 34.98; V: 156.75	**Selection bias: random sequence generation** Stratified blocks: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Coleman, R., Modiano, M. R., Vinholes, J., Pinter, T., Rodriguez-Lescure, A., Colwell, B., Whitlock, P., Provencher, L., Laing, K., Walde, D., Price, C., Hugh, J. C., Childs, B. H., Bassi, K., Lindsay, M. A., Wilson, V., Rupin, M., Houe, V., Vogel, C., Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial, The Lancet Oncology, 14, 72-80, 2013 **Ref Id** 566275 **Country/ies where the study was carried out** International (Europe, North America, South America, Africa, Middle East - countries not specified) **Study type** RCT **Aim of the study** To determine the efficacy of anthracycline and taxane combination chemotherapy compared with standard anthracycline chemotherapy **Study dates**	Age: median 49 Ethnicity: NR **Inclusion criteria** Women aged 18-70; Karnofsky performance scale score ≥80%; surgery (including axillary dissection) with clear margins; positive axillary node involvement **Exclusion criteria** Previous cancer; grade 2+ neuropathy; pregnancy/lactation; serious comorbidities **Reported subgroups** HER2+/-; triple negative	**Control arm:** TAC (docetaxel, doxorubicin and cyclophosphamide)	infusion), followed by 500 mg/m2 IV cyclophosphamide (1-5 minutes), followed by an hour wait, then 75 mg/m2 docetaxel (1 hour IV infusion). Prophylactic dexamethasone and ciprofloxacin were given to prevent hypersensitivity, fluid retention and infection; G-CSF was mandatory in subsequent cycles following an episode of febrile neutropenia. 20 mg tamoxifen was given daily to hormone-receptor positive patients for 5 years; radiotherapy was mandatory after breast conserving surgery and given according to local protocols following mastectomy. **Control arm (anthracycline only):** patients received 6 21-day cycles of FAC: on the first day of each cycle they received 50 mg/m2 doxorubicin (15 minute IV infusion), followed by 500 mg/m2 fluorouracil (15 minute IV infusion), followed by 500 mg/m2 IV cyclophosphamide (1-5 minutes). 20 mg tamoxifen was given daily to hormone-receptor positive patients for 5 years; radiotherapy was mandatory after breast conserving surgery and given according to local protocols following mastectomy.	**OS (10 year follow-up):** O-E: - 30.59; V: 101.58 **Treatment-related morbidities - acute myeloid leukaemia:** taxane + anthracycline 4/744; anthracycline only 1/736 **Treatment-related morbidities - chronic lymphocytic leukaemia:** taxane + anthracycline 0/744; anthracycline only 1/736 **Treatment-related morbidities - myelodysplasia:** taxane + anthracycline 2/744; anthracycline only 1/736 **HER2+ (node positive):** **DFS (10 year follow-up):** O-E: -18.84; V: 36.88 **OS (10 year follow-up):** O-E: -11.93; V: 25.82 **HER2- (node positive):** **DFS (10 year follow-up):** O-E: -10.30; V: 97.78 **OS (10 year follow-up):** O-E: -14.90; V: 70.73	**Selection bias: allocation concealment** 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** 1 patient in the intervention arm and 10 in the control arm did not receive allocated treatment: Low **Selective reporting** Low **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Recruited June 1997 to June 1999 **Source of funding** Sanofi, Saskatchewan Cancer Agency and Aventis				**Triple-negative breast cancer (node positive):** **DFS (10 year follow-up):** O-E: -4.16; V: 23.83 **OS (10 year follow-up):** O-E: -3.89; V: 18.46	BCIRG 001 trial
Full citation Ellis, P., Barrett-Lee, P., Johnson, L., Cameron, D., Wardley, A., O'Reilly, S., Verrill, M., Smith, I., Yarnold, J., Coleman, R., Earl, H., Canney, P., Twelves, C., Poole, C., Bloomfield, D., Hopwood, P., Johnston, S., Dowsett, M., Bartlett, J. M., Ellis, I., Peckitt, C., Hall, E., Bliss, J. M., Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial, The Lancet, 373, 1681-1692, 2009 **Ref Id** 565704 **Country/ies where the study was carried out** UK and Belgium **Study type** RCT	**Sample size** 4,162 **Characteristics** Gender: 100% female Age: mean NR; range NR; 38% 40-49; 36% 50-59; 17% <40; 9% ≥60 Ethnicity: NR **Inclusion criteria** Women aged ≥18; had complete surgical excision; node-positive or high risk node-negative; normal haematological, hepatic and renal function **Exclusion criteria** Locally advanced and/or bilateral breast cancer; pregnant; invasive	**Interventions** **Intervention arm:** 4 cycles of FEC + 4 cycles of docetaxel **Control arm:** 8 cycles of FEC or 4 cycles of epirubicin + 4 cycles of CMF	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 21-day cycles of FEC (600 mg/m2 IV fluorouracil, 60 mg/m2 IV epirubicin and 600 mg/m2 IV cyclophosphamide given on day 1) followed by 4 21-day cycles of 100 mg/m2 IV docetaxel (given as 1 hour infusion on day 1). Patients also received dexamethasone premedication (8mg twice a day for 3 days beginning on the day before docetaxel treatment) and prophylactic ciprofloxacin (500 mg twice a day on days 5-14). 5 years of endocrine therapy (tamoxifen or an aromatase inhibitor) was given to hormone-receptor positive patients for 5 years following chemotherapy. Radiotherapy was mandatory following breast conserving surgery (commencing within 4 weeks of treatment) and given	**Results** **Whole sample:** **DFS (5 year follow-up):** O-E: -13.74; V: 267.93 **Treatment-related morbidity - anaemia:** taxane + anthracycline 13/2073; anthracycline only 14/2089 **Treatment-related morbidity - febrile neutropenia:** taxane + anthracycline 146/2073; anthracycline only 61/2089 **Treatment-related morbidity - neutropenia:** taxane + anthracycline 937/2073; anthracycline only 797/2089 **Treatment-related morbidity - leucopenia:** taxane + anthracycline	**Selection bias: random sequence generation** Computer generated permuted blocks: Low **Selection bias: allocation concealment** 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**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study To determine whether patient outcomes improve following the addition of docetaxel to anthracycline based chemotherapy **Study dates** Randomised February 2001 to July 2003 **Source of funding** Cancer Research UK, Sanofi - Aventis, Pfizer, and Roche	malignancy within last 10 years **Reported subgroups** ER+; ER-; HER2+; HER2-; node negative; node positive; age <60; aged 60+; T1; T2; T3/4		following mastectomy according to local protocols. **Control arm (anthracycline only):** two regimens were used in the control arms: 1) FEC for 8 21-day cycles: 600 mg/m2 IV fluorouracil, 60 mg/m2 IV epirubicin and 600 mg/m2 IV cyclophosphamide given on day 1, or 2) 4 21-day cycles of 100 mg/m2 IV epirubicin (given on day 1) followed by 4 28-day cycles of CMF: 600 mg/m2 IV cyclophosphamide, 40 mg/m2 IV methotrexate and 600 mg/m2 IV fluorouracil given on days 1 and 8 - centres could opt to give 100 mg/m2 oral cyclophosphamide on days 1-14 rather than the IV administrations on days 1 and 8. 5 years of endocrine therapy (tamoxifen or an aromatase inhibitor) was given to hormone-receptor positive patients for 5 years following chemotherapy. Radiotherapy was mandatory following breast conserving surgery (commencing within 4 weeks of treatment) and given following mastectomy according to local protocols.	507/2073; anthracycline only 362/2089 **Treatment-related morbidity - thrombocytopenia:** taxane + anthracycline 12/2073; anthracycline only 27/2089 **Treatment-related morbidity - diarrhoea:** taxane + anthracycline 77/2073; anthracycline only 59/2089 **Treatment-related morbidity - lethargy:** taxane + anthracycline 456/2073; anthracycline only 272/2089 **Treatment-related morbidity - nausea/vomiting:** taxane + anthracycline 199/2073; anthracycline only 205/2089 **Treatment-related morbidity - neuropathy:** taxane + anthracycline 98/2073; anthracycline only 11/2089 **Treatment-related mortality:** taxane + anthracycline 6/2073; anthracycline only 1/2089 **ER+:**	Rates of not commencing treatment (12 people vs 15 people) and discontinuing treatment (390 and 388) were similar between intervention and control arms: Low **Selective reporting** Low **Indirectness** Control: 39% of control arm received chemotherapy that included CMF and the arms were not otherwise equivalent. Harder to draw conclusions about role of taxanes: Serious **Limitations** **Other information** TACT trial; more up-to-date information on OS available in EBCTCG meta-analysis

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				DFS (5 year follow-up): O-E: 3.10; V: 156.63 **ER-:** **DFS (5 year follow-up):** O-E: -15.03; V: 107.94 **HER2+:** **DFS (5 year follow-up):** O-E: -10.24; V: 73.50 **HER2-:** **DFS (5 year follow-up):** O-E: 3.10; V: 156.63 **Node negative:** **DFS (5 year follow-up):** O-E: -3.82; V: 29.85 **Node positive:** **DFS (5 year follow-up):** O-E: -9.44; V: 231.15 **Aged <60:** **DFS (5 year follow-up):** O-E: -9.44; V: 231.15 **Aged 60+:**	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				DFS (5 year follow-up): O-E: -3.15; V: 29.92 **T1:** **DFS (5 year follow-up):** O-E: -8.91; V: 63.99 **T2:** **DFS (5 year follow-up):** O-E: -5.02; V: 164.77 **T3/4:** **DFS (5 year follow-up):** O-E: -3.47; V: 36.75	
Full citation Early Breast Cancer Trialists' Collaborative, Group, Peto, R., Davies, C., Godwin, J., Gray, R., Pan, H. C., Clarke, M., Cutter, D., Darby, S., McGale, P., Taylor, C., Wang, Y. C., Bergh, J., Di Leo, A., Albain, K., Swain, S., Piccart, M., Pritchard, K., Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123	**Sample size** Total sample 101,000 but only interested in individual patient data from the following trials (remaining trials inconsistent with protocol): ADEBAR, BCIRG001, BIG 02-98, CALGB 9344, DEVA, EC-Doc, ECOG E2197, ECTO, HORG, GOIM 9805, GOIM 9902, GOIM 9906, GONO MIG5, MD Anderson, NNCBC 3-Europe, NSAPB B-28,	**Interventions** Interventions grouped into taxane-plus-anthracycline-based regimen vs. the same non-taxane cytotoxic chemotherapy, taxane-plus-anthracycline-based regimen (taxane given sequentially) vs. more (but <doubled) non-taxane cytotoxic chemotherapy, axane-plus-anthracycline-based regimen (taxane given concurrently) vs. more	**Details** No additional information reported	**Results** **FEC/FAC + docetaxel/paclitaxel vs. FEC/FAC:** **OS (follow-up NR):** O-E: 4.17; V: 141.20	**A priori design** Unclear **Duplicate selection/extraction** Not reported: Unclear **Comprehensive literature search** Unclear (information not available in two of the referenced papers and third is unavailable)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
randomised trials, Lancet, 379, 432-44, 2012 **Ref Id** 573043 **Country/ies where the study was carried out** UK **Study type** Meta-analysis of RCTs **Aim of the study** To compare taxane and anthracycline chemotherapy to non-taxane containing chemotherapy **Study dates** Information was sought during 2005-2010 - studies were eligible if they began 1973 to 2003 **Source of funding** Cancer Research UK; British Heart Foundation; UK Medical Research Council	PACS 01, PACS 04, RAPP-01, TACT, Taxit216 **Characteristics** Gender: 100% female Age: NR Ethnicity: NR **Inclusion criteria** All randomised trials that began 1973 to 2003 and compared taxane-based and non-taxane based regimens **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	(but <doubled) non-taxane cytotoxic chemotherapy and taxane-plus-anthracycline-based regimen vs. doubled non-taxane cytotoxic chemotherapy		**AC/EC + paclitaxel/docetaxel vs. AC/EC:** **OS (follow-up NR):** O-E: -59.61; V: 395.26 **Epirubicin + docetaxel/paclitaxel vs. FEC:** **OS (follow-up NR):** O-E: 3.64; V: 42.29 **Doxorubicin + docetaxel vs. AC:** **OS (follow-up NR):** O-E: -5.91; V: 95.50 **Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF vs.**	**Publication status** Grey literature included **List of studies provided** Unclear - trials reported (including those where they could not obtain data) but references to published papers (where available) are not provided **Characteristics of included studies** Basic study characteristics not reported **Quality assessment** Not reported **Impact of quality assessment on conclusions** Not applicable as quality not reported **Appropriate methods for meta-analysis** Unclear - limited information provided about data synthesis **Publication bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				doxorubicin/epirubicin (+/- cyclophosphamide) + CMF: **OS (follow-up NR):** O-E: -13.71; V: 32.99	Not assessed **Conflict of interest** Declaration of interest provided for the review but not included trials **Indirectness** None **Limitations** **Other information**
Full citation Martin, M., Rodriguez-Lescure, A., Ruiz, A., Alba, E., Calvo, L., Ruiz-Borrego, M., Munarriz, B., Rodriguez, C. A., Crespo, C., De Alava, E., Lopez Garcia-Asenjo, J. A., Guitian, M. D., Almenar, S., Gonzalez-Palacios, J. F., Vera, F., Palacios, J., Ramos, M., Gracia Marco, J. M., Lluch, A., Alvarez, I., Segui, M. A., Mayordomo, J. I., Anton, A., Baena, J. M., Plazaola, A., Modolell, A., Pelegri, A., Mel, J. R., Aranda, E., Adrover, E., Alvarez, J. V., Garcia Puche, J. L., Sanchez-Rovira, P., Gonzalez, S., Lopez-Vega, J. M., Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by paclitaxel for early breast cancer, Journal of the	**Sample size** 1,246 **Characteristics** Gender: 100% female Age: median 50; range 23-76 Ethnicity: NR **Inclusion criteria** Women aged 18 to 75; undergone surgery with clear margins and axillary lymph node dissection; adequate bone marrow, liver and renal function **Exclusion criteria**	**Interventions** **Intervention arm:** 4 cycles of FEC followed by 8 cycles of paclitaxel **Control arm:** 6 cycles of FEC	**Details** **Intervention arm (taxane + anthracycline):** Patients received 4 cycles of FEC following the same schedule as the control arm, 3 week break with no treatment, and 8 cycles of weekly paclitaxel (100 mg/m2 administered over 60 minute IV). Tamoxifen was mandatory for hormone receptor positive tumours following chemotherapy (amended to allow aromatase inhibitors for post-menopausal women in September 2005). Radiotherapy was mandatory following breast conserving surgery and administered according to local protocols following mastectomy **Control arm (anthracycline only):** Patients received 6 21-day cycles of FEC - 600 mg/m2	**Results** **Treatment-related morbidity - neutropenia:** taxane + anthracycline 117/614; anthracycline only 161/632 **Treatment-related morbidity - febrile neutropenia:** taxane + anthracycline 31/614; anthracycline only 60/632 **Treatment-related morbidity - peripheral neuropathy:** taxane + anthracycline 159/614; anthracycline only 0/632 (reverted in all patients after treatment concluded) **Treatment-related morbidity - fatigue:** taxane + anthracycline	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to significantly impact results **Detection bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
National Cancer Institute, 100, 805-814, 2008 **Ref Id** 615548 **Country/ies where the study was carried out** Spain **Study type** RCT **Aim of the study** To assess the impact of paclitaxel on disease-free survival **Study dates** Recruited November 1999 to June 2002 **Source of funding** Bristol-Myers Squibb and Pharmacia	Advanced disease (T4 or N2 or N3, or M1); history of other cancers; grade 2+ neuropathy; pregnancy/lactation; serious comorbidities **Reported subgroups** None of interest		5-flourouracil, 90 mg/m2 IV epirubicin and 600 mg/m2 IV cyclophosphamide administered on the first day of each cycle. Tamoxifen was mandatory for hormone receptor positive tumours following chemotherapy (amended to allow aromatase inhibitors for post-menopausal women in September 2005). Radiotherapy was mandatory following breast conserving surgery and administered according to local protocols following mastectomy	15/614; anthracycline only 26/632 **Treatment-related morbidity - nausea:** taxane + anthracycline 33/614; anthracycline only 37/632 **Treatment-related morbidity - vomiting:** taxane + anthracycline 45/614; anthracycline only 63/632	Low due to objective nature of outcomes **Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** **Other information** GEICAM 9906 trial
Full citation Francis, P., Crown, J., Di Leo, A., Buyse, M., Balil, A., Andersson, M., Nordenskjold, B., Lang, I., Jakesz, R., Vorobiof, D., Gutierrez, J., Van Hazel, G., Dolci, S., Jamin, S., Bendahmane, B., Gelber, R. D.,	**Sample size** 2,887 **Characteristics** Gender: 100% female (taken from Oakman 2013)	**Interventions** **Intervention arms:** doxorubicin + docetaxel + CMF (cyclophosphamide, methotrexate and fluorouracil)	**Details** **Intervention arms (taxane + anthracycline):** 1) 3 21-day cycles of 75 mg/m2 doxorubicin followed by 3 21-day cycles of 100 mg/m2 docetaxel followed by 3 cycles of CMF (details not reported).	**Results** **Treatment-related morbidities - febrile neutropenia:** taxane + anthracycline 269/1919; anthracycline only 63/968	**Selection bias: random sequence generation** Stratified minimisation procedure: low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Goldhirsch, A., Castiglione-Gertsch, M., Piccart-Gebhart, M., Adjuvant chemotherapy with sequential or concurrent anthracycline and docetaxel: Breast International Group 02-98 randomized trial [Comment 100(9): 638], Journal of the National Cancer Institute, 100, 121-133, 2008 **Ref Id** 615551 **Country/ies where the study was carried out** International - 21 countries (not specified; taken froom Oakman 2013) **Study type** RCT **Aim of the study** To determine whether incorporating docetaxel into anthracycline-based adjuvant chemotherapy would improve outcomes compared with optimal anthracycline-based adjuvant chemotherapy regimens **Study dates** Randomised June 1998 to June 2001	Age: median 49; range 21-70 Ethnicity: NR **Inclusion criteria** Aged 18-70; node positive; clear surgical margins; within 60 days of surgery; adequate hematologic, renal, liver and cardiac function **Exclusion criteria** Supraclavicular node involvement; previous cancer; grade 2+ neuropathy; serious comorbidities **Reported subgroups** N/A for treatment-related morbidities	**Control arms:** doxorubicin ± cyclophosphamide + CMF	2) 4 21-day cycles of 50 mg/m2 doxorubicin and 75 mg/m2 docetaxel followed by 3 21-day cycles of 100 mg/m2 docetaxel followed by 3 cycles of CMF (details not reported). 5 years of tamoxifen was indicated for hormone-receptor positive patients following chemotherapy and radiotherapy was indicated for those that had breast-conserving surgery (and some individuals who had mastectomy according to local protocols). In 2004, the protocol was amended to allow aromatase inhibitors for post-menopausal women and ovarian suppression for pre-menopausal women (taken from Oakman 2013) **Control arms (anthracycline only):** 1) 4 21-day cycles of 75 mg/m2 doxorubicin followed by 3 cycles of CMF (details not reported). 2) 4 21-day cycles of 60 mg/m2 doxorubicin and 600 mg/m2 of cyclophosphamide followed by 3 cycles of CMF (details not reported). 5 years of tamoxifen was indicated for hormone-receptor positive patients following chemotherapy and radiotherapy was indicated for those that had breast-conserving surgery (and some individuals who had mastectomy according to local protocols). In 2004, the	**Treatment-related morbidities - anaemia:** taxane + anthracycline 58/1919; anthracycline only 48/968 **Treatment-related morbidities - thrombocytopenia:** taxane + anthracycline 77/1919; anthracycline only 24/968 **Treatment-related morbidities - allergy:** taxane + anthracycline 25/1919; anthracycline only 0/968 **Treatment-related morbidities - diarrhoea:** taxane + anthracycline 58/1919; anthracycline only 10/968 **Treatment-related morbidities - neurosensory:** taxane + anthracycline 8/1919; anthracycline only 0/968 **Adequate dose intesntiy - dose reductions:** taxane + anthracycline 431/1919; anthracycline only 169/968 **Treatment-related mortality:** taxane + anthracycline 3/1919; anthracycline only 1/968	**Selection bias: allocation concealment** Allocated centrally: 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** 1.2% of control arms and 0.5 % of intervention arms did not commence treatment; 94% of control arms and 92% of intervention arms completed all cycles: Low **Selective reporting** Low **Indirectness** Comparison: control arm 2 includes CMF and non-taxane

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Sanofi-Aventis			protocol was amended to allow aromatase inhibitors for post-menopausal women and ovarian suppression for pre-menopausal women (taken from Oakman 2013)		components not otherwise equivalent - makes difficult to draw firm conclusions about the role of taxanes: serious **Limitations** **Other information** BIG 02-98 trial
Full citation Martin, M., Ruiz, A., Ruiz Borrego, M., Barnadas, A., Gonzalez, S., Calvo, L., Margeli Vila, M., Anton, A., Rodriguez-Lescure, A., Segui-Palmer, M. A., Munoz-Mateu, M., Dorca Ribugent, J., Lopez-Vega, J. M., Jara, C., Espinosa, E., Mendiola Fernandez, C., Andres, R., Ribelles, N., Plazaola, A., Sanchez-Rovira, P., Salvador Bofill, J., Crespo, C., Carabantes, F. J., Servitja, S., Chacon, J. I., Rodriguez, C. A., Hernando, B., Alvarez, I., Carrasco, E., Lluch, A., Fluorouracil, doxorubicin, and cyclophosphamide (FAC) versus FAC followed by weekly paclitaxel as adjuvant therapy for high-risk, node-negative breast cancer: results from the GEICAM/2003-02 study, Journal of clinical oncology, 31, 2593-9, 2013 **Ref Id**	**Sample size** 1,925 **Characteristics** Gender: NR Age: taxane + anthracycline median 51; anthracycline only median 50; range 24-75 Ethnicity: NR **Inclusion criteria** Aged 18-70 years; histologically confirmed negative axillary involvement; presence of at least 1 of the high risk St. Gallen criteria (<35 years, tumour size>2cm, negative hormone-receptors, grade 2 or 3); Karnofsky performance status ≥80%; normal	**Interventions** **Intervention arm:** 4 cycles of FAC (fluorouracil, doxorubicin, cyclophosphamide) followed by 8 weeks of paclitaxel **Control arm:** 6 cycles of FAC (fluorouracil, doxorubicin, cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 21-day cycles of FAC (500 mg/m2 fluorouracil, 50 mg/m2 doxorubicin and 500 mg/m2 cyclophosphamide) followed by 8 weekly administrations of 100 mg/m2 paclitaxel. Antiemetics, corticosteroids and histamine-receptor blockers were given according to local protocols. Endocrine therapy (tamoxifen or aromatase inhibitors) was given for 5 years to hormone receptor positive patients following chemotherapy; radiotherapy was mandated following breast-conserving surgery and given to large (>5cm) tumours following mastectomy in accordance with local protocols.	**Results** **Whole sample (node negative):** **DFS (5 year follow-up):** O-E: -12.83; V: 39.05 **OS (5 year follow-up):** O-E: -4.06; V: 17.23 **Treatment-related morbidities - leukopenia:** taxane + anthracycline 78/931; anthracycline only 93/986 **Treatment-related morbidities - lymphopenia:** taxane + anthracycline 9/931; anthracycline only 10/986 **Treatment-related morbidities - neutropenia:** taxane +	**Selection bias: random sequence generation** Stratified blocks: Low **Selection bias: allocation concealment** 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

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
570942 **Country/ies where the study was carried out** Spain **Study type** RCT **Aim of the study** To determine the safety and efficacy of weekly paclitaxel for the treatment of node-negative breast cancer patients **Study dates** Recruited September 2003 to October 2008 **Source of funding** Bristol-Myers Squibb	organ and bone function; adequate contraception for potentially fertile women. **Exclusion criteria** Prior systemic therapy or radiotherapy for breast cancer; previous anthracycline or taxane use for any malignancy; grade 2+ neurotoxicity; history of cancer within last 10 years (except adequately treated cervical or skin cancer); pregnant or breastfeeding; HER2+ patients after 2005 *disclosure of adjuvant trastuzumab data) **Reported subgroups** All node negative		**Control arm (anthracycline only):** patients received 6 21-day cycles of FAC 500 mg/m2 fluorouracil, 50 mg/m2 doxorubicin and 500 mg/m2 cyclophosphamide). Antiemetics, corticosteroids and histamine-receptor blockers were given according to local protocols. Endocrine therapy (tamoxifen or aromatase inhibitors) were given for 5 years to hormone receptor positive patients following chemotherapy; radiotherapy was mandated following breast-conserving surgery and given to large (>5cm) tumours following mastectomy in accordance with local protocols.	anthracycline 203/931; anthracycline only 250/986 **Treatment-related morbidities - fatigue:** taxane + anthracycline 74/931; anthracycline only 34/986 **Treatment-related morbidities - nausea:** taxane + anthracycline 25/931; anthracycline only 25/986 **Treatment-related morbidities - vomiting:** taxane + anthracycline 40/931; anthracycline only 40/986 **Treatment-related morbidities - sensory neuropathy:** taxane + anthracycline 51/931; anthracycline only 0/986 **Treatment-related mortality:** taxane + anthracycline 2/931; anthracycline only 7/986	**Attrition bias** 21 patients in the intervention arm and 4 patients in the control arm did not receive the treatment they were allocated to; 119 patients in the intervention arm and 29 patients in the control arm did not complete assigned treatment: High **Selective reporting** Low **Indirectness** None **Limitations** Survival data is slightly premature as node negative patients tend to have a longer time to recurrence; longer follow-up is needed (and is planned) **Other information** GEICAM/2003-02 trial
Full citation	**Sample size** 1,999	**Interventions** **Intervention arm:** FEC (fluorouracil, epirubicin	**Details** **Intervention arm (taxane + anthracycline):** within 42 days	**Results** **Treatment-related morbidity - neutropenia:**	**Selection bias: random sequence generation**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Roche, H., Fumoleau, P., Spielmann, M., Canon, J. L., Delozier, T., Serin, D., Symann, M., Kerbrat, P., Soulie, P., Eichler, F., Viens, P., Monnier, A., Vindevoghel, A., Campone, M., Goudier, M. J., Bonneterre, J., Ferrero, J. M., Martin, A. L., Geneve, J., Asselain, B., Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial, Journal of clinical oncology, 24, 5664-71, 2006 **Ref Id** 571856 **Country/ies where the study was carried out** France and Belgium **Study type** RCT **Aim of the study** To determine optimal doses of epirubicin and docetaxel for a six cycle-regimen that would limit adverse affects **Study dates** Recruited June 1997 to March 2000	**Characteristics** Gender: 100% female Age: median 50, range 25-67 Ethnicity: NR **Inclusion criteria** Aged 18-64 years; had undergone surgery (including axillary dissection) with clear margins; histologically proven axillary lymph node involvement; WHO performance criteria <2; adequate hematologic, hepatic and cardiac function **Exclusion criteria** Pregnancy; cardiac disease contraindicating anthracyclines; previous cancer (except treated skin cancer or cervical cancer); previous radiotherapy, hormone therapy or chemotherapy for breast cancer; >42 days since initial breast cancer surgery **Reported subgroups**	and cyclophosphamide) + docetaxel **Control arm:** FEC (fluorouracil, epirubicin and cyclophosphamide)	of surgery patients commenced 3 21-day cycles of FEC100 - 500 mg/m2 fluorouracil, 100 mg/m2 epirubicin and 500 mg/m2 cyclophosphamide on day 1. This was followed by 3 21-day of 100 mg/m2 docetaxel administered on day 1. Following chemotherapy, hormone-receptor positive patients received 5 years of tamoxifen; for hormone-receptor negative patients, tamoxifen was given according to physician discretion for post-menopausal patients and prohibited for pre-menopausal patients. Radiotherapy was mandated within 4 weeks of the final chemotherapy cycle for those that had breast conserving surgery (taken from Coudert 2012) **Control arm (antracycline only):** within 42 days of surgery patients commenced 6 21-day cycles of FEC100 - 500 mg/m2 fluorouracil, 100 mg/m2 epirubicin and 500 mg/m2 cyclophosphamide on day 1. Following chemotherapy, hormone-receptor positive patients received 5 years of tamoxifen; for hormone-receptor negative patients, tamoxifen was given according to physician discretion for post-menopausal patients and prohibited for pre-menopausal patients. Radiotherapy was mandated within 4 weeks of	taxane + anthracycline 281/1,001; anthracycline only 334/995 **Treatment-related morbidity - febrile neutropenia:** taxane + anthracycline 112/1,001; anthracycline only 84/995 **Treatment-related morbidity - anaemia:** taxane + anthracycline 7/1,001; anthracycline only 14/995 **Treatment-related morbidity - thrombocytopenia:** taxane + anthracycline 4/1,001; anthracycline only 3/995 **Treatment-related morbidity - nausea/vomiting:** taxane + anthracycline 112/1,001; anthracycline only 204/995	Not reported: Unclear **Selection bias: allocation concealment** 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** 97% of control arm completed 6 cycles and 96.1% of intervention arm: Low **Selective reporting** Low **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Sanofi-Aventis and Pfizer	N/A for treatment-related morbidities		the final chemotherapy cycle for those that had breast conserving surgery (taken from Coudert 2012)		PACS 01 trial
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, 27, 2474-2481, 2009 **Ref Id** 615879 **Country/ies where the study was carried out** Europe (countries not specified) **Study type** RCT **Aim of the study**	**Sample size** Total 1,355 - excluding neoadjuvant treatment N=904 **Characteristics** Gender: 100% female Age: NR Ethnicity: NR **Inclusion criteria** Aged ≥18 years; operable breast cancer >2cm in diameter; known hormonal receptor status and grade; Karnofsky performance >70; adequate bone marrow, renal, liver and cardiac function; normal blood pressure **Exclusion criteria** Pregnant or nursing; prior cancer; cardiac arrhythmias, congestive heart failure of recent myocardial infarction;	**Interventions** **Intervention arm:** paclitaxel + doxorubicin + CMF (cyclophosphamide, methotrexate and fluorouracil) **Control arm:** doxorubicin + CMF (cyclophosphamide, methotrexate and fluorouracil)	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 21-day cycles of 60 mg/m2 doxorubicin immediately followed by 200 mg/m2 paclitaxel (3-hour infusion). This was followed by 4 28-day cycles of CMF - 600 mg/m2 IV cyclophosphamide, 40 mg/m2 IV methotrexate and 600 mg/m2 IV fluorouracil on days 1 and 8. Radiotherapy was required for all patients who had breast conserving surgery (compared with mastectomy) and patients who were hormone-receptor positive were offered tamoxifen. **Control arm (anthracycline only):** patients received 4 21-day cycles of 75 mg/m2 IV doxorubicin followed by 4 28-day cycles of CMF - 600 mg/m2 IV cyclophosphamide, 40 mg/m2 IV methotrexate and 600 mg/m2 IV fluorouracil on days 1 and 8. Radiotherapy was required for all patients who had breast conserving surgery (compared with mastectomy) and patients who	**Results** **OS (median follow-up 76 months):** O-E: -6.79; V: 30.41 **DFS (median follow-up 76 months):** O-E: -17.11; V: 54.36	**Selection bias: random sequence generation** Stratified minimisation algorithm: Low **Selection bias: allocation concealment** Centrally allocated: 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** 19 people did not start treatment in intervention arm and 36 discontinued; 9 did not receive treatment in

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To determine the effect of adding paclitaxel to anthracycline-based adjuvant chemotherapy. Further aim to compare this regimen with the same given as neoadjuvant treatment - outside protocol for this question. **Study dates** Recruited November 1996 to May 2002 **Source of funding** Bristol Myers Squibb	active infection; pre-existing neuropathy; psychiatric disorder preventing informed consent **Reported subgroups** None of interest		were hormone-receptor positive were offered tamoxifen.		control arm and 42 discontinued treatment: Low **Selective reporting** Low **Indirectness** None **Limitations** **Other information** ECTO trial
Full citation Coombes, R. C., Bliss, J. M., Espie, M., Erdkamp, F., Wals, J., Tres, A., Marty, M., Coleman, R. E., Tubiana-Mathieu, N., Den Boer, M. O., Wardley, A., Kilburn, L. S., Cooper, D., Thomas, M. W. K., Reise, J. A., Wilkinson, K., Hupperets, P., Randomized, phase III trial of sequential epirubicin and docetaxel versus epirubicin alone in postmenopausal patients with node-positive breast cancer, Journal of Clinical Oncology, 29, 3247-3254, 2011 **Ref Id**	**Sample size** 803 **Characteristics** Gender: 100% female Age: median/range NR; 48% 50-59; 42% 60-69; 7% 70-79; 3% <50 Ethnicity: NR **Inclusion criteria** Post-menopausal women; node positive; normal hematologic,	**Interventions** **Intervention arm:** 3 cycles of epirubicin and 3 cycles of docetaxel **Control arm:** 6 cycles epirubicin	**Details** **Intervention arm (taxane + anthracycline):** patients received 3 28-day cycles of 50 mg/m2 epirubicin given on days 1 and 8, followed by 3 21-day cycles of 100 mg/m2 administered on day 1 (1 hour infusion) and 8mg dexamethasone twice daily for 3 days. G-CSF and antibiotics were recommended following incidences of febrile neutropenia **Control arm (anthracycline only):** patients received 6 28-day cycles of 50 mg/m2	**Results** **Whole sample (node positive):** **DFS (median follow-up 65 months):** O-E: -18.92; V: 49.07 **OS (median follow-up 65 months):** O-E: -12.50; V: 30.09 **Treatment-related morbidities - anaemia:** taxane + anthracycline 126/396; anthracycline only 125/377	**Selection bias: random sequence generation** Computer generated permuted blocks: Low **Selection bias: allocation concealment** Independent random assignment: Low **Selection bias: overall judgement** Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
615909 **Country/ies where the study was carried out** Europe (5 countries - not specified) **Study type** RCT **Aim of the study** To determine the efficacy of epirubicin followed by docetaxel compared with epirubicin alone in post-menopausal patients with node-positive breast cancer **Study dates** 1997 to 2005 **Source of funding** Pfizer and Sanofi-Aventis	hepatic, renal and cardiac function **Exclusion criteria** History of malignancy **Reported subgroups** All node positive; ER+; ER-; T1; T2; T3/4		epirubicin given on days 1 and 8.	**Treatment-related morbidities - acute myeloid leukemia:** taxane + anthracycline 0/396; anthracycline only 1/377 **Treatment-related morbidities - febrile neutropenia:** taxane + anthracycline 51/396; anthracycline only 7/377 **Treatment-related morbidities - leukopenia:** taxane + anthracycline 99/396; anthracycline only 83/377 **Treatment-related morbidities - neutropenia:** taxane + anthracycline 54/396; anthracycline only 54/377 **Treatment-related morbidities - thrombocytopenia:** taxane + anthracycline 1/396; anthracycline only 3/377 **Treatment-related morbidities - diarrhoea:** taxane + anthracycline 70/396; anthracycline only 21/377 **Treatment-related morbidities - lethargy:** taxane + anthracycline 25/396; anthracycline only 15/377	**Performance bias** No blinding but unlikely to have a significant impact **Detection bias** Low due to objective nature of outcomes for treatment-related morbidities and survival outcomes; high for HRQoL outcomes **Attrition bias** 2 patients in experimental arm and 7 in the control arm did not start assigned treatment; 40 patients in experimental arm and 39 patients in control arm did not complete 6 cycles of treatment **Selective reporting** Low **Indirectness** None **Limitations** **Other information** DEVA trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Treatment-related morbidities - nausea/vomiting: taxane + anthracycline 179/396; anthracycline only 211/377 **Treatment-related morbidities - peripheral neuropathy:** taxane + anthracycline 52/396; anthracycline only 8/377 **Treatment-related morbidities - other neurological:** taxane + anthracycline 67/396; anthracycline only 35/377 **Adequate dose intensity - received 85% of planned dose-intensity for cycles 1-3:** taxane + anthracycline 384/406; anthracycline only 365/397 **Adequate dose intensity - received 85% of planned dose-intensity for cycles 4-6:** taxane + anthracycline 309/406; anthracycline only 334/397 **HRQoL - change in global health status from baseline (5 year follow-up - as measured by EORTC QOL scales):** taxane + anthracycline N=63, M=-0.26, SD=23.57; anthracycline only N=49, M=-0.51, SD=23.16	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				HRQoL - change in physical functioning from baseline (5 year follow-up - as measured by EORTC QOL scales): taxane + anthracycline N=65, M=2.31, SD=10.12; anthracycline only N=49, M=6.53, SD=11.89 **HRQoL - change in role functioning from baseline (5 year follow-up - as measured by EORTC QOL scales):** taxane + anthracycline N=65, M=-3.85, SD=29.43; anthracycline only N=49, M=-12.24, SD=35.32 **HRQoL - change in emotional functioning from baseline (5 year follow-up - as measured by EORTC QOL scales):** taxane + anthracycline N=64, M=-5.60, SD=26.65; anthracycline only N=49, M=-10.49, SD=21.75 **HRQoL - change in cognitive functioning from baseline (5 year follow-up - as measured by EORTC QOL scales):** taxane + anthracycline N=64, M=4.17, SD=24.85; anthracycline only N=49, M=5.10, SD=28.30	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				HRQoL - change in social functioning from baseline (5 year follow-up - as measured by EORTC QOL scales): taxane + anthracycline N=64, M=-1.04, SD=24.82; anthracycline only N=48, M=-6.60, SD=29.72 **HRQoL - change in fatigue from baseline (5 year follow-up - as measured by EORTC QOL scales):** taxane + anthracycline N=65, M=-3.16, SD=22.88; anthracycline only N=49, M=0.00, SD=24.22 **HRQoL - change in nausea and vomiting from baseline (5 year follow-up - as measured by EORTC QOL scales):** taxane + anthracycline N=65, M=0.26, SD=14.58; anthracycline only N=49, M=1.02, SD=18.76 **HRQoL - change in diarrhoea from baseline (5 year follow-up - as measured by EORTC QOL scales):** taxane + anthracycline N=63, M=-6.35, SD=24.58; anthracycline only N=49, M=-9.52, SD=22.57 **HRQoL - change in body image from baseline (5**	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				year follow-up - as measured by EORTC QOL scales): taxane + anthracycline N=58, M=2.78, SD=29.45; anthracycline only N=45, M=3.15, SD=22.07 **ER+ (node positive):** **DFS (median follow-up 65 months):** O-E: -10.48; V: 29.37 **ER- (node positive):** **DFS (median follow-up 65 months):** O-E: -8.11; V: 16.41 **T1 (node positive):** **DFS (median follow-up 65 months):** O-E: -10.41; V: 15.46 **T2 (node positive):** **DFS (median follow-up 65 months):** O-E: -7.33; V: 26.72 **T3/4 (node positive):** **DFS (median follow-up 65 months):** O-E: -0.26; V: 4.20	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Roy, C., Choudhury, K. B., Pal, M., Saha, A., Bag, S., Banerjee, C., Adjuvant chemotherapy with six cycles of AC regimen versus three cycles of AC regimen followed by three cycles of Paclitaxel in node-positive breast cancer, Indian journal of cancer, 49, 266-71, 2012 **Ref Id** 566139 **Country/ies where the study was carried out** India **Study type** RCT **Aim of the study** To determine whether adding Paclitaxel to a standard adjuvant chemotherapy regimen would prolong time to recurrence and survival **Study dates** Treated July 2007 to January 2010	**Sample size** 50 **Characteristics** Gender: NR Age: mean 45.6; range 18-66 Ethnicity: NR **Inclusion criteria** Aged 20-70; Karnofsky performance status ≥70; post-mastectomy; stage II; positive axillary lymph node involvement; normal haematological and cardiac function **Exclusion criteria** Secondary malignancy; co-morbid disease **Reported subgroups** All node positive	**Interventions** **Intervention arm:** 3 cycles of AC + 3 cycles of paclitaxel **Control arm:** 6 cycles AC (doxorubicin + cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** All patients had modified radical mastectomy within the 4-6 weeks prior to chemotherapy. Patients received 3 21-day cycles of AC (60 mg/m2 doxorubicin and 600 mg/m2 cyclophosphamide) followed by 3 21-day cycles of 165 mg/m2 paclitaxel. Hormone-receptor positive and unknown patients received tamoxifen following chemotherapy. **Control arm (anthracycline only):** All patients had modified radical mastectomy within the 4-6 weeks prior to chemotherapy. Patients received 6 21-day cycles of AC: 60 mg/m2 doxorubicin and 600 mg/m2 cyclophosphamide. Hormone-receptor positive and unknown patients received tamoxifen following chemotherapy.	**Results** **DFS (median follow-up 2 years):** O-E: -4.32; V: 3.54 **OS (median follow-up 2 years):** O-E: -3.79; V: 3.21 **Treatment-related morbidities - nausea:** taxane + anthracycline 19/25; anthracycline only 15/25 **Treatment-related morbidities - vomiting:** taxane + anthracycline 23/25; anthracycline only 24/25 **Treatment-related morbidities - diarrhoea:** taxane + anthracycline 16/25; anthracycline only 8/25 **Treatment-related morbidities - anaemia:** taxane + anthracycline 9/25; anthracycline only 18/25 **Treatment-related morbidities - leukopenia:** taxane + anthracycline 9/25; anthracycline only 12/25	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** 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** No loss to follow-up: Low **Selective reporting** Low **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding No sources reported				**Treatment-related morbidities - thrombocytopenia:** taxane + anthracycline 0/25; anthracycline only 0/25 **Treatment-related morbidities - neurotoxicity:** taxane + anthracycline 3/25; anthracycline only 0/25	None **Limitations** Very limited sample size and follow-up **Other information**
Full citation Delbaldo, C., Serin, D., Mousseau, M., Greget, S., Audhuy, B., Priou, F., Berdah, J. F., Teissier, E., Laplaige, P., Zelek, L., Quinaux, E., Buyse, M., Piedbois, P., Association Europeenne de Recherche en, Oncologie, A phase III adjuvant randomised trial of 6 cycles of 5-fluorouracil-epirubicine-cyclophosphamide (FEC100) versus 4 FEC 100 followed by 4 Taxol (FEC-T) in node positive breast cancer patients (Trial B2000), European journal of cancer, 50, 23-30, 2014 **Ref Id** 570545 **Country/ies where the study was carried out** Europe (countries not specified)	**Sample size** 837 **Characteristics** Gender: 100% female Age: mean 52; 27-78 Ethnicity: NR **Inclusion criteria** Women aged 17+; WHO performance score ≤2; node positive; within 2 months of surgery; adequate hematologic function **Exclusion criteria** Prior chemotherapy or radiotherapy; bilateral, inflammatory or contralateral breast cancer; cardiac history;	**Interventions** **Intervention arm:** 4 cycles of FEC + 4 cycles of paclitaxel **Control arm:** 6 cycles of FEC	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 21-day cycles of FEC: 500 mg/m2 5-fluorouracil (30 minute short infusion), 100 mg/m2 epirubicin (15 minute short infusion) and 500 mg/m2 cyclophosphamide (30 minute short infusion) on day 1. This was immediately followed by 4 21-day cycles of 175 mg/m2 paclitaxel (3 hour IV perfusion); administration was preceded by dexamethasone, diphenhydramine and ranitidine. ER+ and/or PR+ patients received endocrine therapy (tamoxifen or aromatase inhibitors dependent on menopausal status) for 5 years following chemotherapy. **Control arm (anthracycline only):** patients received 6 21-day cycles of FEC: 500 mg/m2	**Results** **DFS (median follow-up 108 months):** O-E: -0.64; V: 63.36 **OS (median follow-up 108 months):** O-E: -6.54; V: 40.26 **Treatment-related morbidities - neutropenia:** taxane + anthracycline 285/377; anthracycline only 337/426 **Treatment-related morbidities - leukopenia:** taxane + anthracycline 26/377; anthracycline only 29/426 **Treatment-related morbidities - febrile neutropenia:** taxane + anthracycline 30/377; anthracycline only 33/426	**Selection bias: random sequence generation** Minimisation procedure: Low **Selection bias: allocation concealment** 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

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study type RCT **Aim of the study** To determine the efficacy and safety of adding paclitaxel to anthracycline-based chemotherapy regimen **Study dates** March 2000 to December 2002 **Source of funding** Bristol Meyers Squibb	pregnancy; breast-feeding; history of malignancy; life expectancy <2 years; contraindications to study drugs; psychiatric morbidity; participating in other trial(s) **Reported subgroups** All node positive		5-fluorouracil (30 minute short infusion), 100 mg/m2 epirubicin (15 minute short infusion) and 500 mg/m2 cyclophosphamide (30 minute short infusion) on day 1. ER+ and/or PR+ patients received endocrine therapy (tamoxifen or aromatase inhibitors dependent on menopausal status) for 5 years following chemotherapy.	**Treatment-related morbidities - thrombocytopenia:** anthracycline 76/377; anthracycline only 88/426 **Treatment-related morbidities - nausea:** taxane + anthracycline 293/377; anthracycline only 349/426 **Treatment-related morbidities - vomiting:** taxane + anthracycline 163/377; anthracycline only 206/426 **Treatment-related morbidities - neuropathy:** taxane + anthracycline 209/377; anthracycline only 18/426 **Treatment-related morbidities - diarrhoea:** taxane + anthracycline 15/377; anthracycline only 21/426 **Treatment-related morbidities - fatigue:** taxane + anthracycline 6/377; anthracycline only 9/426	**Attrition bias** Unclear **Selective reporting** Low **Indirectness** None **Limitations** Insufficiently powered - planned number of patients not reached due to slow accrual **Other information** AERO-B2000 trial
Full citation	**Sample size** 231	**Interventions** **Intervention arm:** 4 cycles of epirubicin and	**Details** **Intervention arm (taxane + anthracycline):** patients	**Results**	**Selection bias: random sequence generation**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Kummel, S., Krocker, J., Kohls, A., Breitbach, G. P., Morack, G., Budner, M., Blohmer, J. U., Elling, D., Randomised trial: Survival benefit and safety of adjuvant dose-dense chemotherapy for node-positive breast cancer, British Journal of Cancer, 94, 1237-1244, 2006 **Ref Id** 572022 **Country/ies where the study was carried out** Germany **Study type** RCT **Aim of the study** To evaluate the survival benefit, feasibility and safety of dose dense, paclitaxel containing chemotherapy for women with node positive breast cancer **Study dates** July 1996 to December 2000 **Source of funding** Amgen, Pfizer and Bristol-Myers Squibb	**Characteristics** Gender: 100% female Age: mean 52.9; SD 9.8; range 26-72 Ethnicity: NR **Inclusion criteria** Women with completely excised (including axillary dissection) breast cancer; at least 4 involved axillary lymph nodes; ECOG performance status <2; adequate organ function and bone marrow reserve; surgery within last 15 days **Exclusion criteria** Previous chemotherapy and/or radiotherapy **Reported subgroups** All node positive	paclitaxel + 3 cycles of CMF (cyclophosphamide, methotrexate and 5-fluorouracil) **Control arm:** 4 cycles of epirubicin and cyclophosphamide + 3 cycles of CMF (cyclophosphamide, methotrexate and 5-fluorouracil)	received 4 14-day cycles of 90 mg/m2 IV epirubicin and 175 mg/m2 paclitaxel (3 hour IV infusion) - both given on day 1. This was followed by 3 14-day cycles of CMF: 600 mg/m2 IV cyclophosphamide, 40 mg/m2 IV methotrexate and 600 mg/m2 IV 5-fluorouacil. Patients also received filgrastim every day during chemotherapy. Hormone-receptor positive patients received 20 mg tamoxifen daily for 5 years; 40-50Gy radiotherapy was following chemotherapy to individuals who had breast conserving surgery. **Control arm (anthracycline only):** patients received 4 21-day cycles of 90 mg/m2 IV epirubicin and 600 mg/m2 IV cyclophosphamide followed by 3 21-day cycles of CMF: 600 mg/m2 IV cyclophosphamide, 40 mg/m2 IV methotrexate and 600 mg/m2 IV 5-fluorouacil. Patients could receive filgrastim if required. Hormone-receptor positive patients received 20 mg tamoxifen daily for 5 years; 40-50Gy radiotherapy was following chemotherapy to individuals who had breast conserving surgery.	**DFS (median follow-up 38 months):** O-E: -6.53; V: 17.66 **OS (median follow-up 38 months):** O-E: -5.03; V: 8.92 **Treatment-related morbidities - grade 3+ leukopenia:** taxane + anthracycline 48/108; anthracycline only 52/108 **Treatment-related morbidities - grade 3+ neutropenia:** taxane + anthracycline 48/108; anthracycline only 53/108 **Treatment-related morbidities - grade 3+ thrombocytopenia:** taxane + anthracycline 3/108; anthracycline only 0/108 **Treatment-related morbidities - grade 3+ anaemia:** taxane + anthracycline 4/108; anthracycline only 1/108 **Treatment-related morbidities - grade 3+ nausea/vomiting:** taxane + anthracycline 7/108; anthracycline only 12/108 **Treatment-related morbidities - grade 3+ fatigue:** taxane +	Computer-generated, permuted blocks **Selection bias: allocation concealment** 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** 4 patients in each arm discontinued treatment: Low **Selective reporting** Low **Indirectness** None **Limitations** Interim report with limited sample size

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				anthracycline 8/108; anthracycline only 3/108 **Treatment-related morbidities - grade 3+ peripheral neuropathy:** taxane + anthracycline 4/108; anthracycline only 0/108	**Other information**
Full citation Janni, W., Harbeck, N., Rack, B., Augustin, D., Jueckstock, J., Wischnik, A., Annecke, K., Scholz, C., Huober, J., Zwingers, T., Friedl, T. W. P., Kiechle, M., Randomised phase III trial of FEC120 vs EC-docetaxel in patients with high-risk node-positive primary breast cancer: Final survival analysis of the ADEBAR study, British Journal of Cancer, 114, 863-871, 2016 **Ref Id** 538294 **Country/ies where the study was carried out** Germany **Study type** RCT **Aim of the study**	**Sample size** 1,493 **Characteristics** Gender: 100% female Age: median 54; range 25-71 Ethnicity: NR **Inclusion criteria** Women aged 18-70; at least 4 involved axillary lymph nodes; surgical excision (including ALND) with clear margins within last 5 weeks; ECOG performance status <2; adequate bone marrow reserve; adequate renal and liver function; life expectancy of at least 32 weeks **Exclusion criteria**	**Interventions** **Intervention arm:** 4 cycles of EC (epirubicin and cyclophosphamide) + 4 cycles of docetaxel **Control arm:** 6 cycles of FEC (5-fluorouracil, epirubicin and cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 21-day cycles of EC (90 mg/m2 IV epirubicin and 600 mg/m2 IV cyclophosphamide on day 1) followed by 4 21-day cycles of 100 mg/m2 IV docetaxel (administered on day 1). Patients with hormone-receptor positive breast cancer received endocrine therapy (tamoxifen or an aromatase inhibitor) for 5 years following chemotherapy; adjuvant radiotherapy was administered after completion of, or in some cases after 50% of, chemotherapy. No primary prohphylactic treatmeant was given but secondary prophylaxis was permitted following neutropenia or insufficient leukocytes. **Control arm (anthracycline only):** patients received 6 28-day cycles of FEC120: 500 mg/m2 IV 5-fluorouracil and 60 mg/m2 IV epirubicin given on	**Results** **Whole sample (node positive):** **DFS (median follow-up 5 years):** O-E: 13.46; V: 102.17 **Treatment-related morbidities - grade 3+ anaemia:** anthracycline + taxane 19/684; anthracycline only 105/674 **Treatment-related morbidities - grade 3+ leukopenia:** anthracycline + taxane 491/684; anthracycline only 542/674 **Treatment-related morbidities - grade 3+ neutropenia:** anthracycline + taxane 406/684; anthracycline only 420/674 **Treatment-related morbidities - grade 3+ thrombocytopenia:**	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** 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**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To determine the efficacy and tolerability of adding docetaxel to an anthracycline containing chemotherapy regimen for women with high-risk, node-negative breast cancer **Study dates** September 2001 - May 2005 **Source of funding** Novartis, GSK, Amgen, Eisai, Roche, Teva, Pierre Fabre, Janssen Diagnostics, Sanofi-Aventis, Astra-Zeneca,	Inflammatory breast cancer; previous cancer treatment; other malignancy (except in situ cervical and skin cancer); cardiac morbidities affecting left ventricular function; myocardial infarction, angina pectoris or uncontrolled arterial hypertension within the last 6 months; pregnant or breastfeeding; hypersensitivity to any of the study medications **Reported subgroups** All patients node positive; HER2+; HER2-; triple negative		days 1 and 8; 75 mg/m2 oral cyclophosphamide given on days 1-14. Patients with hormone-receptor positive breast cancer received endocrine therapy (tamoxifen or an aromatase inhibitor) for 5 years following chemotherapy; adjuvant radiotherapy was administered after completion of, or in some cases after 50% of, chemotherapy.	anthracycline + taxane 13/684; anthracycline only 160/674 **Treatment-related morbidities - grade 3+ nausea:** anthracycline + taxane 8/684; anthracycline only 11/674 **Treatment-related morbidities - grade 3+ vomiting:** anthracycline + taxane 24/684; anthracycline only 12/674 **Treatment-related morbidities - grade 3+ diarrhoea:** anthracycline + taxane 7/684; anthracycline only 12/674 **Treatment-related morbidities - grade 3+ neurological symptoms:** anthracycline + taxane 5/684; anthracycline only 1/674 **Treatment-related morbidities - grade 3+ allergic reactions:** anthracycline + taxane 1/684; anthracycline only 0/674 **Adequate dose intensity - reduction in first half of cycles:** anthracycline + taxane 3/689; anthracycline only 22/675	10 patients in experimental arm and 7 patients in control arm did not start assigned treatment; 84 patients in experimental arm and 113 in control arm did not complete treatment: Unclear **Selective reporting** Low **Indirectness** None **Limitations** **Other information** ADEBAR trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Adequate dose intensity - reduction in second half of cycles: anthracycline + taxane 35/689; anthracycline only 64/675 **HER2+ (node positive):** **DFS (median follow-up 5 years):** O-E: 4.22; V: 27.92 **HER2- (node positive):** **DFS (median follow-up 5 years):** O-E: 3.71; V: 65.86 **Triple negative (node positive):** **DFS (median follow-up 5 years):** O-E: -2.88; V: 20.72	
Full citation Polyzos, A., Malamos, N., Boukovinas, I., Adamou, A., Ziras, N., Kalbakis, K., Kakolyris, S., Syrigos, K., Papakotoulas, P., Kouroussis, C., Karvounis, N., Vamvakas, L., Christophyllakis, C., Athanasiadis, A., Varthalitis, I., Georgoulias, V., Mavroudis, D., FEC versus sequential docetaxel followed by	**Sample size** 756 **Characteristics** Gender: 100% female Age: median 56, range 26-73 Ethnicity: NR	**Interventions** **Intervention arm:** docetaxel + epirubicin + cyclophosphamide **Control arm:** 5-flourouracil + epirubicin + cyclophosphamide	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 21-day cycles of 100 mg/m2 IV docetaxel (one hour infusion with routine steroid premedication for 3 days, starting the day before treatment) followed by 4 21-day cycles of EC - 75 mg/m2 IV epirubicin and 700 mg/m2 IV cyclophosphamide. All patients	**Results** **Whole sample (node positive, cardiac disease absent):** **DFS (5 year follow-up):** O-E: -15.35; V: 56.43 **OS (5 year follow-up):** O-E: -3.57; V: 32.73	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Allocated centrally: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
epirubicin/cyclophosphamide as adjuvant chemotherapy in women with axillary node-positive early breast cancer: A randomized study of the Hellenic Oncology Research Group (HORG), Breast cancer research and treatment, 119, 95-104, 2010 **Ref Id** 565859 **Country/ies where the study was carried out** Greece and Cyprus **Study type** RCT **Aim of the study** To determine the role of docetaxel in node positive early breast cancer **Study dates** June 1995 to October 2004 **Source of funding** No sources reported	**Inclusion criteria** Women aged 18-75; surgical excision (breast conserving surgery or mastectomy and axillary lymph node dissection) with clear margins within last 60 days; involved axillary lymph nodes; ECOG performance status 0-2; adequate hematologic, hepatic and cardiac (as measured by left ventricular ejection fraction) function **Exclusion criteria** Pregnancy; cardiac disease contraindicating anthracyclines; previous cancer; other serious morbidities; prior chemotherapy, hormone therapy or radiation **Reported subgroups** All node positive, cardiac disease absent; ER+/-		treated with breast-conserving surgery received radiotherapy following chemotherapy; radiotherapy was given at the physician's discretion in high risk cases following mastectomy. ER and/or PR positive patients received 20 mg tamoxifen daily for 5 years. **Control arm (anthracycline only):** patients received 6 21-day cycles of FEC - 700 mg/m2 IV 5-flourouracil, 75 mg/m2 IV epirubicin and 700 mg/m2 IV cyclophosphamide. All patients treated with breast-conserving surgery received radiotherapy following chemotherapy; radiotherapy was given at the physician's discretion in high risk cases following mastectomy. ER and/or PR positive patients received 20 mg tamoxifen daily for 5 years.	**Adequate dose intensity - dose reduction:** taxane + anthracycline 66/378; anthracycline only 48/378 **Treatment-related morbidities - neutropenia:** taxane + anthracycline 273/378; anthracycline only 160/378 **Treatment-related morbidities - febrile neutropenia:** taxane + anthracycline 29/378; anthracycline only 11/378 **Treatment-related morbidities - anaemia:** taxane + anthracycline 5/378; anthracycline only 3/378 **Treatment-related morbidities - thrombocytopenia:** taxane + anthracycline 0/378; anthracycline only 2/378 **Treatment-related morbidities - nausea (grade 3/4):** taxane + anthracycline 23/378; anthracycline only 18/378 **Treatment-related morbidities - diarrhoea (grade 3/4):** taxane + anthracycline 14/378; anthracycline only 0/378	**Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to significantly impact results: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** 32 people did not receive allocated treatment and 13 didn't receive full treatment according to protocol - rates similar between arms: Low **Selective reporting** Low **Indirectness** None **Limitations** Study accrual was slow and took 9 years to complete - may have introduced heterogeneity; underpowered to detect differences

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Treatment-related morbidities - hypersensitivity: taxane + anthracycline 4/378; anthracycline only 0/378 **Treatment-related mortality:** taxane + anthracycline 0/378; anthracycline only 2/378 **ER+ (node positive, cardiac disease absent):** **DFS (5 year follow-up):** O-E: - 5.23; V: 8.00 **ER- (node positive, cardiac disease absent):** **DFS (5 year follow-up):** O-E: -4.37; V: 6.13	**Other information** HORG trial
Full citation Martin, M., Rodriguez-Lescure, A., Ruiz, A., Alba, E., Calvo, L., Ruiz-Borrego, M., Santaballa, A., Rodriguez, C. A., Crespo, C., Abad, M., Dominguez, S., Florian, J., Llorca, C., Mendez, M., Godes, M., Cubedo, R., Murias, A., Batista, N., Garcia, M. J., Caballero, R., de Alava, E., Molecular predictors of efficacy of adjuvant weekly paclitaxel in early breast cancer, Breast Cancer	**Sample size** 1,246 **Characteristics** Gender: 100% female (taken from Martin 2008) Age: median 50; range 23-76 (taken from Martin 2008) Ethnicity: NR **Inclusion criteria**	**Interventions** **Intervention arm:** 4 cycles of FEC followed by 8 cycles of paclitaxel **Control arm:** 6 cycles of FEC	**Details** **Intervention arm (taxane + anthracycline):** Patients received 4 cycles of FEC following the same schedule as the control arm, 3 week break with no treatment, and 8 cycles of weekly paclitaxel (100 mg/m2 administered over 60 minute IV). Tamoxifen was mandatory for hormone receptor positive tumours following chemotherapy (amended to allow aromatase inhibitors for post-menopausal	**Results** **DFS (7 year follow-up):** O-E: -24.85; V: 86.40 **OS (7 year follow-up):** O-E: - 15.93; V: 52.89	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Research & Treatment, 123, 149-57, 2010 **Ref Id** 570941 **Country/ies where the study was carried out** Spain **Study type** RCT **Aim of the study** To evaluate the effect of molecular subtypes on paclitaxel response **Study dates** Recruited November 1999 to June 2002 (taken from Martin 2008) **Source of funding** Bristol-Myers Squibb and Pharmacia	Women aged 18 to 75; undergone surgery with clear margins and axillary lymph node dissection; adequate bone marrow, liver and renal function (taken from Martin 2008) **Exclusion criteria** Advanced disease (T4 or N2 or N3, or M1); history of other cancers; grade 2+ neuropathy; pregnancy/lactation; serious comorbidities (taken from Martin 2008) **Reported subgroups** Insufficient presentation of results for subgroups of interest		women in September 2005). Radiotherapy was mandatory following breast conserving surgery and administered according to local protocols following mastectomy (taken from Martin 2008) **Control arm (anthracycline only):** Patients received 6 21-day cycles of FEC - 600 mg/m2 5-flourouracil, 90 mg/m2 IV epirubicin and 600 mg/m2 IV cyclophosphamide administered on the first day of each cycle. Tamoxifen was mandatory for hormone receptor positive tumours following chemotherapy (amended to allow aromatase inhibitors for post-menopausal women in September 2005). Radiotherapy was mandatory following breast conserving surgery and administered according to local protocols following mastectomy (taken from Martin 2008) ER/PR status initially scored according to Allred method but reclassified to ER+/PR+ if staining occurred in ≥1% of nuclei to aid comparison with BCIRG001 results. HER2 statues evaluated by FISH and positive result defined as gene:chromosone 17 >2		**Performance bias** No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** **Other information** GEICAM 9906 trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Del Mastro, L., Levaggi, A., Michelotti, A., Cavazzini, G., Adami, F., Scotto, T., Piras, M., Danese, S., Garrone, O., Durando, A., Accortanzo, V., Bighin, C., Miglietta, L., Pastorino, S., Pronzato, P., Castiglione, F., Landucci, E., Conte, P. F., Bruzzi, P., 5-Fluorouracil, epirubicin and cyclophosphamide versus epirubicin and paclitaxel in node-positive early breast cancer: a phase-III randomized GONO-MIG5 trial, Breast Cancer Research and Treatment, 155, 117-126, 2016 **Ref Id** 616685 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To compare an anthracycline and paclitaxel containing regimen with an anthracycline containing regimen as adjuvant therapy for high risk breast cancer patients	**Sample size** 1,055 **Characteristics** Gender: 100% female Age: mean NR; range NR; 39% <50; 31% 50-59; 30% >59 Ethnicity: NR **Inclusion criteria** Women who had undergone surgery including full ipsilateral axillary dissection; 1-10 involved axillary lymph nodes; aged less than 70 years; adequate hematologic, hepatic and renal function; within 5 weeks of surgery. **Exclusion criteria** Prior chemotherapy **Reported subgroups** All node positive; age <60; age 60+; T1-2; T3-4	**Interventions** **Intervention arm:** 4 cycles of EP (epirubicin and paclitaxel) **Control arm:** 6 cycles of FEC (5-Fluorouracil, epirubicin and cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 21-day cycles of EP (90 mg/m2 epirubicin and 175 mg/m2 paclitaxel given as a 3-hour infusion on day 1); patients also received 20 mg dexamethasone, 40 mg orphenadrine and 50 mg ranitidine before paclitaxel. 5 years of tamoxifen (20 mg/day) was given to post-menopausal women, and to ER and/or PR positive, pre-menopausal women. Radiotherapy was mandatory following breast conserving surgery and given following mastectomy according to local protocols. **Control arm (anthracycline only):** patients received 6 21-day cycles of FEC (600 mg/m2 5-fluorouracil, 60 mg/m2 epirubicin and 600 mg/m2 cyclophosphamide IV on day 1). 5 years of tamoxifen (20 mg/day) was given to post-menopausal women, and to ER and/or PR positive, pre-menopausal women. Radiotherapy was mandatory following breast conserving surgery and given following mastectomy according to local protocols.	**Results** **Whole sample (node positive):** **DFS (10 year follow-up):** O-E: 6.49; V: 131.76 **OS (10 year follow-up):** O-E: -6.96; V: 69.87 **Treatment-related morbidities - anaemia:** taxane + anthracycline 1/516; anthracycline only 0/500 **Treatment-related morbidities - leukopenia:** taxane + anthracycline 91/516; anthracycline only 86/500 **Treatment-related morbidities - neutropenia:** taxane + anthracycline 11/516; anthracycline only 15/500 **Treatment-related morbidities - febrile neutropenia:** taxane + anthracycline 0/516; anthracycline only 0/500 **Treatment-related morbidities - thrombocytopenia:** taxane + anthracycline 4/516; anthracycline only 13/500	**Selection bias: random sequence generation** Permuted blocks: Low **Selection bias: allocation concealment** 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** Similar rates of discontinued treatment and loss to follow-up across arms: Low **Selective reporting** Low **Indirectness** None

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Recruited November 1996 to January 2001 **Source of funding** Bristol Myers Squibb				**Treatment-related morbidities - lymphoma:** taxane + anthracycline 0/516; anthracycline only 1/500 **Treatment-related morbidities - acute leukemia:** taxane + anthracycline 1/516; anthracycline only 0/500 **Treatment-related morbidities - nausea/vomiting:** taxane + anthracycline 21/516; anthracycline only 39/500 **Treatment-related morbidities - diarrhoea:** taxane + anthracycline 1/516; anthracycline only 2/500 **Treatment-related morbidities - allergic reaction:** taxane + anthracycline 3/516; anthracycline only 1/500 **Treatment-related morbidities - neurological:** taxane + anthracycline 4/516; anthracycline only 0/500 **Adequate dose-intensity - dose reductions and/or treatment delays:** taxane + anthracycline 94/535; anthracycline only 177/520	**Limitations** Treatment duration shorter in experimental compared with control arm; paclitaxel was given over a 3 week cycle - subsequent trials have shown weekly paclitaxel to be more effective; under-powered due to a lower number of events than expected **Other information** GONO-MIG5 trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Age <60 (node positive): **OS (10 year follow-up):** O-E: -8.35; V: 47.90 **Age 60+ (node positive):** **OS (10 year follow-up):** O-E: -2.54; V: 26.91 **T1-2 (node positive):** **OS (10 year follow-up):** O-E: -8.37; V: 65.49 **T3-4 (node positive):** **OS (10 year follow-up):** O-E: -0.62; V: 4.43	
Full citation Albert, J. M., Buzdar, A. U., Guzman, R., Allen, P. K., Strom, E. A., Perkins, G. H., Woodward, W. A., Hoffman, K. E., Tereffe, W., Hunt, K. K., Buchholz, T. A., Oh, J. L., Prospective randomized trial of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) versus paclitaxel and FAC (TFAC) in patients with operable breast cancer: impact of taxane chemotherapy on locoregional control, Breast Cancer Research & Treatment, 128, 421-7, 2011	**Sample size** 511 **Characteristics** Gender: 100% female Age: mean 49; range 22-80 Ethnicity: NR **Inclusion criteria** Histologically confirmed, T1-3, N0-1, M0 invasive breast cancer (taken	**Interventions** **Intervention arm:** 4 cycles of paclitaxel and 4 cycles of FAC **Control arm:** 8 cycles of FAC	**Details** **Intervention arm (Taxane + anthracycline):** Patients received 4 cycles of paclitaxel - 250 mg/m2 as continuous IV infusion over 24 hours given every 3 weeks. This was followed by 4 cycles of FAC - 500 mg/m2 5-Flourouracil IV on days 1 and 4, 50 mg/m2 doxorubicin continuous IV infusion over 72 hours (days 1 to 3) and 500 mg/m2 cyclophosphamide IV on day 1; cycle repeated every 3-4 weeks. Patients who were aged 50 years or over and ER+	**Results** **Whole sample:** **LRR (including distant metastases; median follow-up 124 months):** O-E: -3.39; V: 9.04 **OS (median follow-up 124 months):** O-E: -0.44; V: 25.09 **Node positive:** **LRR (including distant metastases; median**	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Ref Id 570306 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To determine whether adding paclitaxel to a doxorubicin regimen improves locoregional control **Study dates** Recruited 1994 to 1998 **Source of funding** No sources reported	from Albert 2011); adequate bone-marrow function, liver function and renal function (taken from Buzdar 2002) **Exclusion criteria** Uncompensated congestive heart failure, previous invasive cancer except localised skin cancer or in situ cervical cancer (taken from Buzdar 2002) **Reported subgroups** Positive nodal involvement		subsequently received tamoxifen for 5 years. **Control arm (anthracycline only):** Patients received 8 cycles of FAC - 500 mg/m2 5-Flourouracil IV on days 1 and 4, 50 mg/m2 doxorubicin continuous IV infusion over 72 hours (days 1 to 3) and 500 mg/m2 cyclophosphamide IV on day 1; cycle repeated every 3-4 weeks. Patients who were aged 50 years or over and ER+ subsequently received tamoxifen for 5 years.	**follow-up 124 months):** O-E: -1.84; V: 6.96 **OS (median follow-up 124 months):** O-E: -1.56; V: 19.92	No blinding, but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** Low **Selective reporting** Low **Indirectness** Intervention: 32% received the first 4 cycles of chemotherapy as neoadjuvant therapy (rates equivalent between arms): Serious; local and distant relapse reported instead of DFS: serious **Limitations** May be underpowered to detect small differences in locoregional recurrence **Other information** Trial conducted at MD Anderson Cancer Centre

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Jacquemier, J., Boher, J. M., Roche, H., Esterni, B., Serin, D., Kerbrat, P., Andre, F., Finetti, P., Charafe-Jauffret, E., Martin, A. L., Campone, M., Viens, P., Birnbaum, D., Penault-Llorca, F., Bertucci, F., Protein expression, survival and docetaxel benefit in node-positive breast cancer treated with adjuvant chemotherapy in the FNCLCC-PACS 01 randomized trial, Breast Cancer Research, 13, R109, 2011 **Ref Id** 611646 **Country/ies where the study was carried out** France and Belgium **Study type** RCT **Aim of the study** To assess the impact of immunohistochemical markers on the DFS benefit of docetaxel **Study dates** Enrolled June 1997 to March 2000 (taken from Coudert 2012)	**Sample size** 1,099 **Characteristics** Gender: 100% female (taken from Coudert 2012) Age: NR Ethnicity: NR **Inclusion criteria** Women aged 18 to 64 with node positive unilateral breast cancer; undergone surgery with clear margins and axillary dissection; WHO performance status <2; adequate renal, hepatic and cardiac function (taken from Coudert 2012). Had tumour block representative of the primary tumour collected **Exclusion criteria** History of cardiac disease that contraindicated anthracycline use (taken from Coudert 2012) **Reported subgroups**	**Interventions** **Intervention arm:** 3 cycles of FEC100 followed by 3 cycles of docetaxel (taken from Coudert 2012) **Control arm:** 6 cycles of FEC100 (taken from Coudert 2012)	**Details** **Intervention arm (taxane + anthracycline):** within 42 days of surgery patients commenced 3 21-day cycles of FEC100 - 500 mg/m2 fluorouracil, 100 mg/m2 epirubicin and 500 mg/m2 cyclophosphamide on day 1. This was followed by 3 21-day of 100 mg/m2 docetaxel administered on day 1. Following chemotherapy, hormone-receptor positive patients received 5 years of tamoxifen; for hormone-receptor negative patients, tamoxifen was given according to physician discretion for post-menopausal patients and prohibited for pre-menopausal patients. Radiotherapy was mandated within 4 weeks of the final chemotherapy cycle for those that had breast conserving surgery (taken from Coudert 2012) **Control arm (antracycline only):** within 42 days of surgery patients commenced 6 21-day cycles of FEC100 - 500 mg/m2 fluorouracil, 100 mg/m2 epirubicin and 500 mg/m2 cyclophosphamide on day 1. Following chemotherapy, hormone-receptor positive patients received 5 years of tamoxifen; for hormone-receptor negative patients, tamoxifen was given according to physician discretion for post-	**Results** **Triple negative:** **DFS (5 year follow-up):** O-E: -1.45; V: 11.33	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** 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** NR specifically for this subgroup; judged as low based on Coudert 2012 **Selective reporting** Low **Indirectness** None

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Ligue Nationale Contre le Cancer	Triple negative		menopausal patients and prohibited for pre-menopausal patients. Radiotherapy was mandated within 4 weeks of the final chemotherapy cycle for those that had breast conserving surgery (taken from Coudert 2012) HER2 status was evaluated with the Dako scale; HER2+ was defined as IHC score 3+, or 2+ with Fluorescent In Situ Hybridisation (FISH) amplification		**Limitations** **Other information** PACS01 trial
Full citation Schwentner, L., Harbeck, N., Singer, S., Eichler, M., Rack, B., Forstbauer, H., Wischnik, A., Scholz, C., Huober, J., Friedl, T. W. P., Weissenbacher, T., Hartl, K., Kiechle, M., Janni, W., Fink, V., Short term quality of life with epirubicin-fluorouracil-cyclophosphamid (FEC) and sequential epirubicin/cyclophosphamid-docetaxel (EC-DOC) chemotherapy in patients with primary breast cancer - Results from the prospective multi-center randomized ADEBAR trial, Breast, 27, 69-77, 2016 **Ref Id** 616740 **Country/ies where the study was carried out**	**Sample size** 1,306 **Characteristics** Gender: 100% female Age: median 54; range 25-71 (taken from Janni 2016) Ethnicity: NR **Inclusion criteria** Women aged 18-70; complete resection (including axillary dissection) with clear margins; ECOG performance status <2; adequate bone marrow; N2-3 **Exclusion criteria**	**Interventions** **Intervention arm:** 4 cycles of EC (epirubicin and cyclophosphamide) + 4 cycles of docetaxel **Control arm:** 6 cycles of FEC (5-fluorouracil, epirubicin and cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 21-day cycles of EC (90 mg/m2 IV epirubicin and 600 mg/m2 IV cyclophosphamide on day 1) followed by 4 21-day cycles of 100 mg/m2 IV docetaxel (administered on day 1). Patients with hormone-receptor positive breast cancer received endocrine therapy (tamoxifen or an aromatase inhibitor) for 5 years following chemotherapy; adjuvant radiotherapy was administered after completion of, or in some cases after 50% of, chemotherapy. No primary prohphylactic treatmeant was given but secondary prophylaxis was permitted following neutropenia or insufficient leukocytes (taken from Janni 2016).	**Results** **HRQoL - Global health (as measured by EORTC QLQ-C30 4 weeks after chemotherapy):** taxane + anthracycline N=305, M=49.5, SD=22.2; anthraycline only N=263, M=53.0, SD=20.6 **HRQoL - Physical functioning (as measured by EORTC QLQ-C30 4 weeks after chemotherapy):** taxane + anthracycline N=311, M=66.8, SD=22.0; anthraycline only N=265, M=71.1, SD=19.4 **HRQoL - Nausea & vomiting (as measured by EORTC QLQ-C30 4 weeks after chemotherapy):** taxane + anthracycline N=310,	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to significantly impact results **Detection bias** High due to subjective outcomes

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Germany **Study type** RCT **Aim of the study** To assess health-related quality of life as a secondary outcome of the ADEBAR trial **Study dates** March 2002 to May 2005 **Source of funding** Amgen, Astra Zeneca, Novartis, Sanovi-Aventis, and Wilex	Inflammatory breast cancer; concurrent chemotherapy; secondary malignancies; cardiac comorbidities; contraindications to study medications; pregnancy **Reported subgroups** All node positive		**Control arm (anthracycline only):** patients received 6 28-day cycles of FEC120: 500 mg/m2 IV 5-fluorouracil and 60 mg/m2 IV epirubicin given on days 1 and 8; 75 mg/m2 oral cyclophosphamide given on days 1-14. Patients with hormone-receptor positive breast cancer received endocrine therapy (tamoxifen or an aromatase inhibitor) for 5 years following chemotherapy; adjuvant radiotherapy was administered after completion of, or in some cases after 50% of, chemotherapy (taken from Janni 2016).	M=9.1, SD=18.8; anthraycline only N=265, M=13.4, SD=21.5 **HRQoL - Fatigue (as measured by EORTC QLQ-C30 4 weeks after chemotherapy):** taxane + anthracycline N=311, M=55.1, SD=26.0; anthraycline only N=265, M=50.3, SD=25.6 **HRQoL - Systemic therapy side effects (as measured by EORTC QLQ-BR23 4 weeks after chemotherapy):** taxane + anthracycline N=307, M=48.4, SD=20.9; anthraycline only N=259, M=42.9, SD=20.0	**Attrition bias** 10 patients in experimental arm and 7 patients in control arm did not start assigned treatment; 84 patients in experimental arm and 113 in control arm did not complete treatment: Unclear (taken from Janni 2016) **Selective reporting** Low **Indirectness** None **Limitations** **Other information** ADEBAR trial
Full citation Vici, P., Brandi, M., Giotta, F., Foggi, P., Schittulli, F., Di Lauro, L., Gebbia, N., Massidda, B., Filippelli, G., Giannarelli, D., Di Benedetto, A., Mottolese, M., Colucci, G., Lopez, M., A multicenter phase III prospective randomized trial of high-dose epirubicin in combination with cyclophosphamide (EC) versus	**Sample size** 750 **Characteristics** Gender: NR Age: taxane + anthracycline median 50; anthracycline only median 51 Ethnicity: NR	**Interventions** **Intervention arm:** epirubicin + cyclophosphamide + docetaxel **Control arm:** epirubicin + cyclophosphamide	**Details** **Intervention arm (taxane+anthracycline):** Patients received 100 mg/m2 docetaxel over 1 hour IV infusion on the first day of 4 21-day cycles; this was followed by 4 21-day cycles of EC - 120 mg/m2 epirubicin and 600 mg/m2 IV cyclophosphamide on day 1. Following chemotherapy, radiotherapy	**Results** **Whole sample (node positive):** **OS (median follow-up 64 months):** O-E: -3.41; V: 19.56 **DFS (median follow-up 64 months):** O-E: -0.50; V: 49.40	**Selection bias: random sequence generation** Stratified computer generated minimisation procedure: Low **Selection bias: allocation concealment**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
docetaxel followed by EC in node-positive breast cancer. GOIM (Gruppo Oncologico Italia Meridionale) 9902 study, Annals of Oncology, 23, 1121-9, 2012 **Ref Id** 571332 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To compare the efficacy of adding docetaxel to EC chemotherapy **Study dates** April 1999 to October 2005 **Source of funding** Sanofi-Aventis and Gruppo Oncologico Italia Meridionale	**Inclusion criteria** Aged 18-70; surgery (including axillary dissection) within previous 6 weeks; histologically proven axillary involvement; WHO performance status <2; adequate hematologic, hepatic, renal and cardiac function **Exclusion criteria** Pregnancy; previous systemic therapy or radiotherapy; previous cancer; cardiac disease contraindicating anthracyclines; comorbid neuropathy or other severe morbidities **Reported subgroups** All node positive; T1, T2/3; ER+/-; HER2+/-		was given following breast conserving surgery or in the case of 4 or more positive nodes; ER and/or PR positive individuals received 5 years of tamoxifen. **Control arm (anthracycline only):** Patients received 4 21-day cycles of EC - 120 mg/m2 epirubicin and 600 mg/m2 IV cyclophosphamide on day 1. Following chemotherapy, radiotherapy was given following breast conserving surgery or in the case of 4 or more positive nodes; ER and/or PR positive individuals received 5 years of tamoxifen. ER and PR status were evaluated histochemically and considered positive when 10% of cells showed reactivity; HER2 status was evaluated using the DAKO Hercept Test kit and FISH.	**Treatment-related morbidity - neutropenia:** taxane + anthracycline 233/363; anthracycline only 192/354 **Treatment-related morbidity - neutropenic fever:** taxane + anthracycline 24/363; anthracycline only 10/354 **Treatment-related morbidity - anemia:** taxane + anthracycline 7/363; anthracycline only 9/354 **Treatment-related morbidity - thrombocytopenia:** taxane + anthracycline 4/363; anthracycline only 2/354 **Treatment-related morbidity - nausea/vomiting:** taxane + anthracycline 21/363; anthracycline only 21/354 **Treatment-related morbidity - diarrhea:** taxane + anthracycline 12/363; anthracycline only 1/354 **Treatment-related morbidity - neurological:** taxane + anthracycline 12/363; anthracycline only 0/354	Centralised at coordination centre: Low **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to significantly impact results: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** 88% if intervention arm and 94% of control arm received complete treatment as specified in protocol: Unclear **Selective reporting** Low **Indirectness** None **Limitations** May be underpowered due to relatively small sample size and fewer events than expected

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Treatment-related morbidity - hypersensitivity: taxane + anthracycline 19/363; anthracycline only 1/354 **T1:** **DFS (median follow-up 64 months):** O-E: 1.59; V: 15.22 **T2/T3:** **DFS (median follow-up 64 months):** O-E: -1.75; V: 34.14 **ER+:** **DFS (median follow-up 64 months):** O-E: 4.12; V: 31.41 **ER-:** **DFS (median follow-up 64 months):** O-E: -5.73; V: 17.45 **HER2+:** **DFS (median follow-up 64 months):** O-E: 0.72; V: 9.31	**Other information** GOIM 9902 trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				HER2-: **DFS (median follow-up 64 months):** O-E: 4.81; V: 14.92	
Full citation Oakman, C., Francis, P. A., Crown, J., Quinaux, E., Buyse, M., De azambuja, E., vila, M. M., Andersson, M., Nordenskjold, B., Jakesz, R., Thurlimann, B., Gutierrez, J., Harvey, V., Punzalan, L., Dell'Orto, P., Larsimont, D., Steinberg, I., Gelber, R. D., Piccart-Gebhart, M., Viale, G., Di Leo, A., Overall survival benefit for sequential doxorubicin-docetaxel compared with concurrent doxorubicin and docetaxel in node-positive breast cancer-8-year results of the breast international group 02-98 phase III trial, Annals of Oncology, 24, 1203-1211, 2013 **Ref Id** 552556 **Country/ies where the study was carried out** International - 21 countries (not specified) **Study type** RCT	**Sample size** Total sample size 2,887 **Characteristics** Gender: 100% female Age: median 49 Ethnicity: NR **Inclusion criteria** Women aged 18-70; positive axillary lymph nodes **Exclusion criteria** Major comorbidities **Reported subgroups** All patients node positive; ER+ (luminal A and B groups combined); HER2+; triple negative	**Interventions** **Intervention arms:** doxorubicin + docetaxel + CMF (cyclophosphamide, methotrexate and fluorouracil) **Control arms:** doxorubicin ± cyclophosphamide + CMF	**Details** **Intervention arms (taxane + anthracycline):** 1) 3 21-day cycles of 75 mg/m2 doxorubicin followed by 3 21-day cycles of 100 mg/m2 docetaxel followed by 3 cycles of CMF (details not reported). 2) 4 21-day cycles of 50 mg/m2 doxorubicin and 75 mg/m2 docetaxel followed by 3 21-day cycles of 100 mg/m2 docetaxel followed by 3 cycles of CMF (details not reported). 5 years of tamoxifen was indicated for hormone-receptor positive patients following chemotherapy and radiotherapy was indicated for those that had breast-conserving surgery (and some individuals who had mastectomy according to local protocols). In 2004, the protocol was amended to allow aromatase inhibitors for post-menopausal women and ovarian suppression for pre-menopausal women. **Control arms (anthracycline only):** 1) 4 21-day cycles of 75 mg/m2 doxorubicin followed by 3 cycles of CMF (details not reported). 2) 4 21-day cycles of	**Results** **Whole sample (node positive):** **DFS (median 8 year follow-up):** O-E: -19.60; V: 207.79 **OS (median 8 year follow-up):** O-E: -12.66; V: 134.24 **ER+ (node positive):** **DFS (median 8 year follow-up) - comparison with sequential docetaxel arm only:** O-E: -11.54; V: 58.17 **HER2+ (node positive):** **DFS (median 8 year follow-up) - comparison with sequential docetaxel arm only:** O-E: -4.55; V: 8.10 **Triple negative (node positive):**	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** 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** Not reported: Unclear **Selective reporting** Low **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study To examine the impact of docetaxel on disease-free survival **Study dates** Recruited June 1998 to June 2001 **Source of funding** Sanofi-Aventis and Associazione Italiana Ricerca Cancro (AIRC), Milan, Italy			60 mg/m2 doxorubicin and 600 mg/m2 of cyclophosphamide followed by 3 cycles of CMF (details not reported). 5 years of tamoxifen was indicated for hormone-receptor positive patients following chemotherapy and radiotherapy was indicated for those that had breast-conserving surgery (and some individuals who had mastectomy according to local protocols). In 2004, the protocol was amended to allow aromatase inhibitors for post-menopausal women and ovarian suppression for pre-menopausal women.	**DFS (median 8 year follow-up) - comparison with sequential docetaxel arm only:** O-E: -1.44; V: 13.67	Comparison: control arm 2 includes CMF and non-taxane components not otherwise equivalent - makes difficult to draw firm conclusions about the role of taxanes: serious **Limitations** Small sample sizes in subgroup analysis **Other information** BIG 02-98 trial
Full citation Nitz, U., Gluz, O., Huober, J., Kreipe, H. H., Kates, R. E., Hartmann, A., Erber, R., Scholz, M., Lisboa, B., Mohrmann, S., Mobus, V., Augustin, D., Hoffmann, G., Weiss, E., Bohmer, S., Kreienberg, R., Du Bois, A., Sattler, D., Thomssen, C., Kiechle, M., Janicke, F., Wallwiener, D., Harbeck, N., Kuhn, W., Final analysis of the prospective WSG-AGO EC-Doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: efficacy and predictive value of Ki67 expression, Annals of	**Sample size** Total 2,012 - only interested in intervention arm and FEC control arm (N=1,773) **Characteristics** Gender: NR Age: taxane + anthracycline median 52; anthracycline only median 51.5 Ethnicity: NR **Inclusion criteria** 18-65; T1-3 with 1-3 positive lymph nodes;	**Interventions** **Intervention arm:** 4 cycles of EC (epirubicin + cyclophosphamide) + 4 cycles of docetaxel **Control arm:** 6 cycles of FEC (5-fluorouracil, epirubicin + cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 21-day of 90 mg/m2 IV epirubicin and 600 mg/m2 IV cyclophosphamide followed by 4-21 day cycles of 100 mg/m2 IV docetael; G-CSF was recommended at the start of taxane therapy. **Control arm (anthracycline only):** patients received 6 21-day cycles of FEC: 500 mg/m2 IV 5-fluorouracil, 100 mg/m2 IV epirubicin and 500 mg/m2 IV cyclophosphamide.	**Results** **EFS (5 year follow-up):** O-E: -14.55; V: 49.20 **OS (5 year follow-up):** O-E: -8.90; V: 24.96 **Treatment-related morbidities - febrile neutropenia:** taxane + anthracycline 36/978; anthracycline only 17/795	**Selection bias: random sequence generation** Stratified permuted blocks: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
OncologyAnn Oncol, 25, 1551-7, 2014 **Ref Id** 567251 **Country/ies where the study was carried out** Germany **Study type** RCT **Aim of the study** To evaluate the efficacy of taxane-based chemotherapy in patients with node-positive breast cancer **Study dates** April 2000 to August 2005 **Source of funding** Amgen and Sanofi-Aventis	clear surgical margins and >10 axillary lymph nodes removed; ECOG performance status <2; within 6 weeks of surgery **Exclusion criteria** Major organ dysfunction; peripheral neuropathy; pregnancy; inflammatory breast cancer **Reported subgroups** All patients node positive				No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** 81% of intervention arm and 89% of control arm completed treatment according to protocol: High **Selective reporting** Insufficient presentation of HRQoL results **Indirectness** Outcomes: Event-free survival reported instead of DFS: serious **Limitations** **Other information** EC-Doc trial
Full citation Henderson, I. C., Berry, D. A., Demetri, G. D., Cirrincione, C. T., Goldstein, L. J., Martino, S., Ingle,	**Sample size** 3,121	**Interventions** **Intervention arm:** doxorubicin +	**Details** **Intervention arm (taxane + anthracycline):** Chemotherapy commenced with 84 days of	**Results** **Recurrence (median follow-up 69 months):** O-E: -50.03; V: 268.49	**Selection bias: random sequence generation**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
J. N., Cooper, M. R., Hayes, D. F., Tkaczuk, K. H., Fleming, G., Holland, J. F., Duggan, D. B., Carpenter, J. T., Frei, E., 3rd, Schilsky, R. L., Wood, W. C., Muss, H. B., Norton, L., Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer, Journal of clinical oncology, 21, 976-83, 2003 **Ref Id** 572540 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To determine whether a higher dose of doxorubicin and/or adding paclitaxel to chemotherapy prolongs time to recurrence and survival **Study dates** Randomised May 1994 to April 1999	**Characteristics** Gender: 100% female Age: mean NR; range NR; 21% <40 years; 40% 40-49 years; 27% 50-59 years; 12% ≥60 years Ethnicity: 83% Caucasian; 10% Black **Inclusion criteria** Breast cancer with involved axillary nodes that had clear surgical margins following mastectomy or breast-conserving surgery (including axillary lymph node sampling). **Exclusion criteria** No additional criteria reported **Reported subgroups** All node positive	cyclyophosphamide + paclitaxel **Control arm:** doxorubicin + cyclyophosphamide	surgery. All patients received 600 mg/m2 IV cyclophosphamide on day1 for 4 21-day cycles; patients were randomised to receive either 60 mg/m2 doxorubicin on day 1 of each cycle, 75 mg/m2 doxorubicin on days 1 and 2 of each cycle, or 90 mg/m2 of doxorubicin on days 1 and 2 of each cycle. Patients then received 175 mg/m2 paclitaxel for 4 21-day cycles. Filgrastim and ciprofloxacin were given to patients receiving 90 mg/m2 of doxorubicin after febrile neutropenia occurred in some patients. Radiotherapy was required following chemotherapy for all patients who had breast-conserving surgery; 94% of ER and/or PR positive patients received tamoxifen for 5 years. **Control arm (anthracycline only):** Chemotherapy commenced with 84 days of surgery. All patients received 600 mg/m2 IV cyclophosphamide on day1 for 4 21-day cycles; patients were randomised to receive either 60 mg/m2 doxorubicin on day 1 of each cycle, 75 mg/m2 doxorubicin on days 1 and 2 of each cycle, or 90 mg/m2 of doxorubicin on days 1 and 2 of each cycle. Filgrastim and ciprofloxacin were given to patients receiving 90 mg/m2 of doxorubicin after febrile		Stratified permuted block: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to significantly impact results: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** 4% of intervention arm didn't start paclitaxel and 8% of those that started did not complete 4 cycles; 2% of control arm did not complete 4 samples: Unclear **Selective reporting** Insufficient presentation of treatment-related morbidities **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding The National Cancer Institute and Bristol-Myers Squibb			neutropenia occurred in some patients. Radiotherapy was required following chemotherapy for all patients who had breast-conserving surgery; 94% of ER and/or PR positive patients received tamoxifen for 5 years.		Outcome: recurrence reported instead of DFS **Limitations** **Other information** CALGB 9344 trial; more up-to-date information on OS available in EBCTCG meta-analysis
Full citation Brain, E. G., Bachelot, T., Serin, D., Kirscher, S., Graic, Y., Eymard, J. C., Extra, J. M., Combe, M., Fourme, E., Nogues, C., Rouesse, J., Life-threatening sepsis associated with adjuvant doxorubicin plus docetaxel for intermediate-risk breast cancer, JamaJama, 293, 2367-71, 2005 **Ref Id** 680709 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study**	**Sample size** 627 **Characteristics** Gender: 100% female Age: taxane + anthracycline median 53;anthracycline only 52; range 26-70 Ethnicity: NR **Inclusion criteria** Women aged 18-70; surgical resection (including axillary dissection) with clear margins; high risk node negative or limited (≤3) node positive	**Interventions** **Intervention arm:** 4 cycles of doxorubicin + docetaxel **Control arm:** 4 cycles of AC (doxorubicin + cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** patients received 4 cycles of 50 mg/m2 doxorubicin + 75 mg/m2 docetaxel. No further details reported **Control arm (anthracycline only):** patients received 4 cycles of 60 mg/m2 doxorubicin + 600 mg/m2 cyclophosphamide. No further details reported	**Results** **Treatment-related morbidity - febrile neutropenia:** taxane + anthracycline 126/311; anthracycline only 22/316 **Treatment-related morbidity - grade 3+ nausea/vomiting:** taxane + anthracycline 17/311; anthracycline only 30/316 **Treatment-related morbidity - grade 3+ diarrhoea:** taxane + anthracycline 9/311; anthracycline only 2/316	**Selection bias: random sequence generation** Computerised random number generator: Low **Selection bias: allocation concealment** Allocation concealed but method not specified: Unclear **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to significantly impact results **Detection bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To investigate adverse events associated with adjuvant chemotherapy for breast cancer **Study dates** Treated June 1999 to January 2003 **Source of funding** René Huguenin Cancer Centre, Aventis, Ligue Régionale Contre le Cancer du Département des Yvelines	**Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest				Low due to objective nature of outcomes **Attrition bias** Not reported: Unclear **Selective reporting** Low **Indirectness** None **Limitations** **Other information** RAPP-01
Full citation Mamounas, E. P., Bryant, J., Lembersky, B., Fehrenbacher, L., Sedlacek, S. M., Fisher, B., Wickerham, D. L., Yothers, G., Soran, A., Wolmark, N., Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 23, 3686-3696, 2005 **Ref Id** 611910	**Sample size** 3,060 **Characteristics** Gender: NR Age: mean/range NR; 36% 40-49; 31% 50-59; 19% ≥60; 14% ≤39 Ethnicity: 85% Caucasian; 8% Black **Inclusion criteria** Undergone lumpectomy (including axillary dissection) with clear	**Interventions** **Intervention arm:** 4 cycles of AC (doxorubicin + cyclophosphamide) + 4 cycles of paclitaxel **Control arm:** 4 cycles of AC (doxorubicin + cyclophosphamide)	**Details** **Intervention arm (taxane + anthracycline):** 4 21-day cycles of AC (60 mg/m2 slow IV infusion of doxorubicin + 600 mg/m2 IV cyclophosphamide) followed by 4 21-day cycles of 225 mg/m2 paclitaxel as a 3-hour infusion. Patients received premedication with dexamethasone, diphenhydramine and cimetidine or ranitidine. Hormone receptor positive patients, and those aged over 50, also received 20 mg tamoxifen daily for 5 years commencing at the start of	**Results** **DFS (5 year follow-up):** O-E: -39.51; V: 214.60 **Treatment-related mortality:** taxane + anthracycline 2/243 ; anthracycline only 5/255	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA **Study type** RCT **Aim of the study** To determine whether the addition of paclitaxel to AC chemotherapy will prolong disease-free survival and overall survival **Study dates** August 1995 to May 1998 **Source of funding** National Cancer Institute, Department of Health and Human Services, National Institutes of Health (NIH), Bethesda, MD	margins, or modified radical mastectomy; node positive; adequate hematologic, hepatic and renal function; ≥10 year life expectancy **Exclusion criteria** Previous history of breast cancer; prior radiotherapy, chemotherapy, immunotherapy or hormonal therapy for breast cancer **Reported subgroups** All node positive		chemotherapy. Radiotherapy was mandated following breast conserving surgery and not permitted following mastectomy. **Control arm (anthracycline only):** 4 21-day cycles of AC (60 mg/m2 slow IV infusion of doxorubicin + 600 mg/m2 IV cyclophosphamide). Hormone receptor positive patients, and those aged over 50, also received 20 mg tamoxifen daily for 5 years commencing at the start of chemotherapy. Radiotherapy was mandated following breast conserving surgery and not permitted following mastectomy.		No blinding but unlikely to significantly impact results **Detection bias** Low due to objective nature of outcomes **Attrition bias** 98% of control arm and 76% of intervention arm completed all cycles of chemotherapy: High **Selective reporting** Low **Indirectness** None **Limitations** **Other information** NSABP B-28; more up-to-date information on OS available in EBCTCG meta-analysis

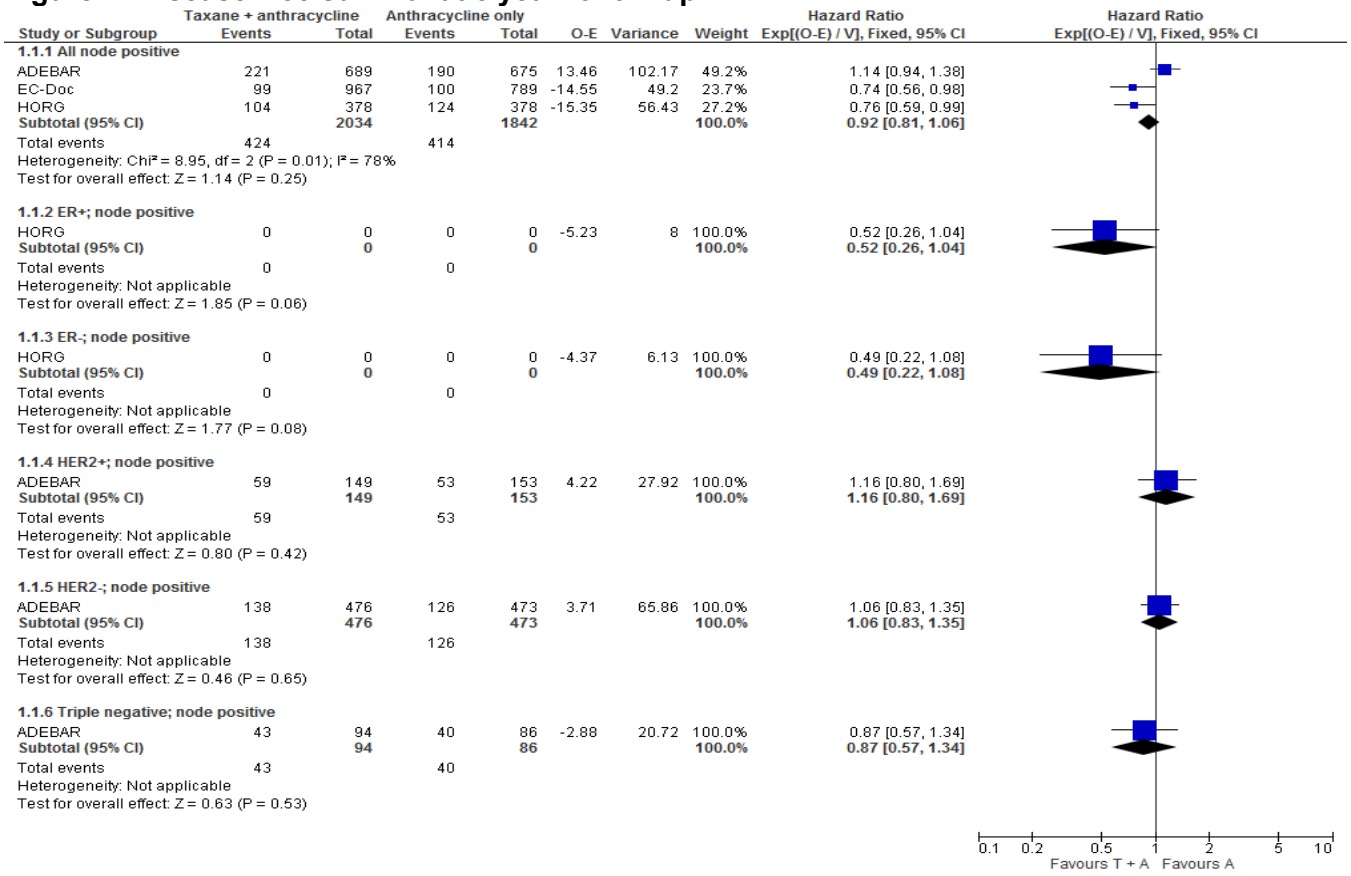
AC, doxorubicin, cyclophosphamide; AERO, Association Europèenne de Recherche en Oncologie; ALND, axillary lymph node dissection; BCIRG, Breast Cancer International Research Group; CALGB, Cancer and Leukemia Group B; CMF, cyclophosphamide, methotrexate, fluorouracil; DEVA, docetaxel epirubicin adjuvant trial; DFS, disease-free survival; EC, epirubicin, cyclophosphamide; Ec-Doc, epirubicin docetaxel trial; ECOG, Eastern Cooperative Oncology Groupl; ECTO, European Cooperative Trial in Operable Breast Cancer; EORTC, European Organisation for Research and Treatment of Cancer; EP, epirubicin, paclitaxel; ER, oestrogen receptor; FAC, fluorouracil, doxorubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; FISH, fluorescent in situ hybridization; G-CSF, granulocyte colony-stimulating factor; GEICAM, Grupo Español de Investigación en Cáncer de Mama; GOIM, Gruppo Oncologico Italia Meridionale; GONO-MIG5, Gruppo Oncologico Nord-Ovest - Mammella Intergruppo Group 5; HER2, human epidermal growth factor receptor 2; HORG, Hellenic Oncology Research Group; HRQoL, health-related quality of life; IHC, immunohistochemical; IV, intravenous; LRR, locoregional recurrence; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; PR, progesterone receptor;

QoL, quality of life; RAPP, Risk Assessment and Prevention Program; SD, standard deviation; TAC, docetaxel, doxroubcin, cyclophosphamide; WHO, World Health Organisation

Appendix E – Forest plots

Comparison 1. EC + docetaxel versus FEC

Figure 2: Disease-free survival at 5 year follow-up



Note. Number of events and participants in each arm not reported for oestrogen receptor (ER) subgroups

Figure 3: Overall survival at 5 year follow-up

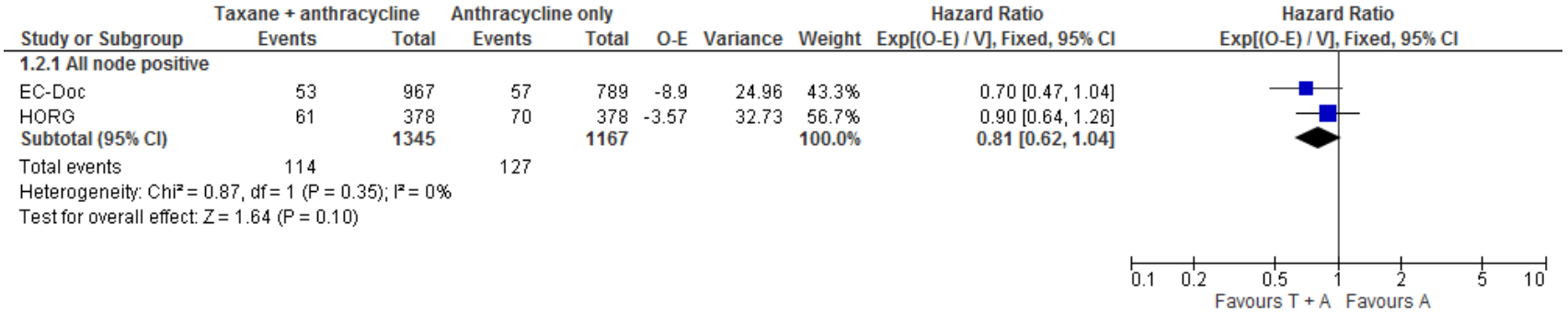


Figure 4: Treatment-related morbidity: neutropenia at 5 year follow-up

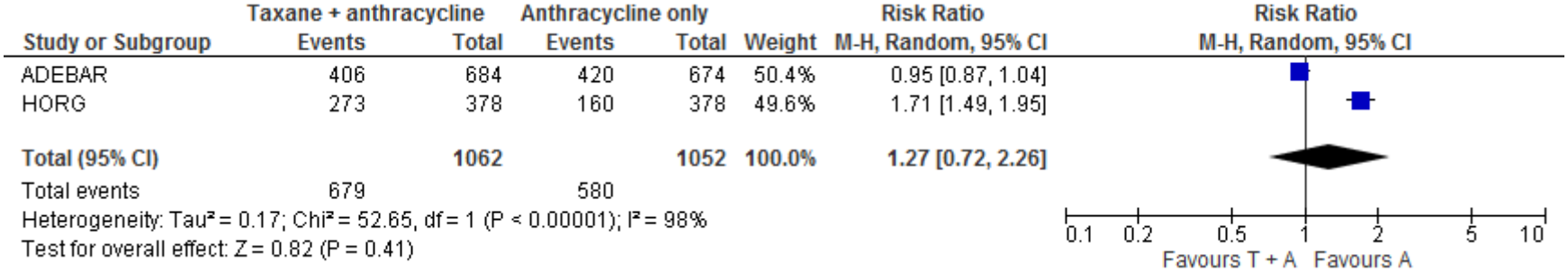


Figure 5: Treatment-related morbidity: febrile neutropenia at 5 year follow-up

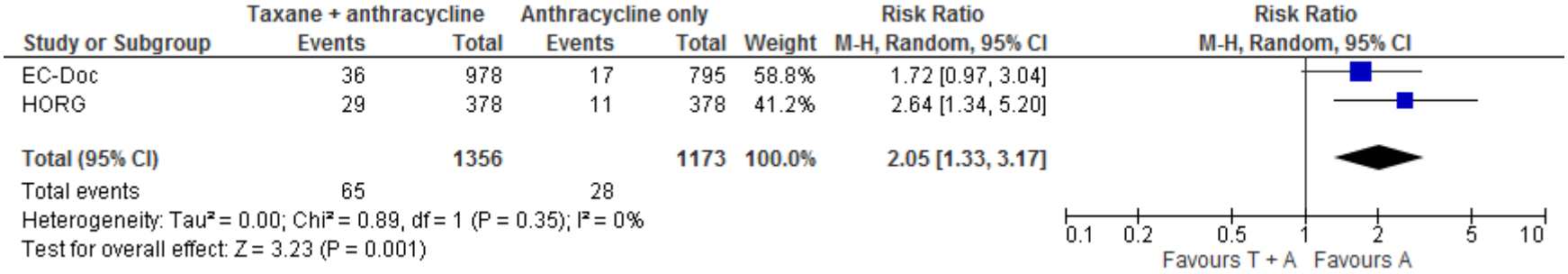


Figure 6: Treatment-related morbidity: anaemia at 5 year follow-up

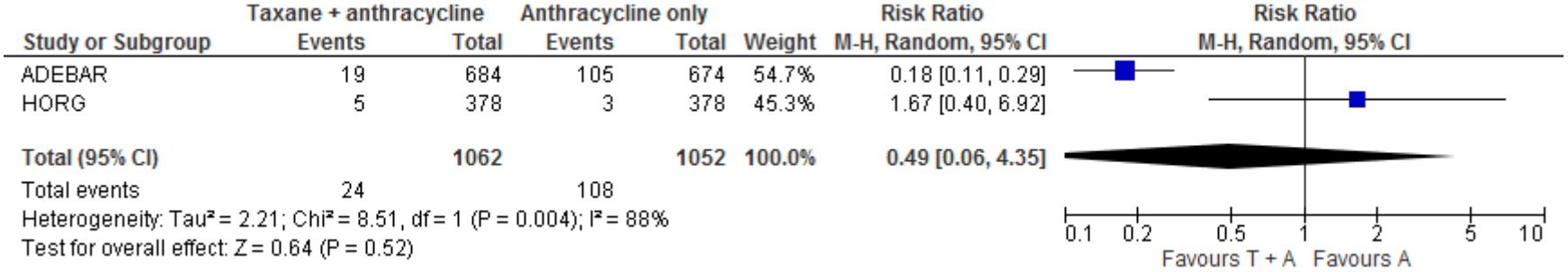


Figure 7: Treatment-related morbidity: thrombocytopenia at 5 year follow-up

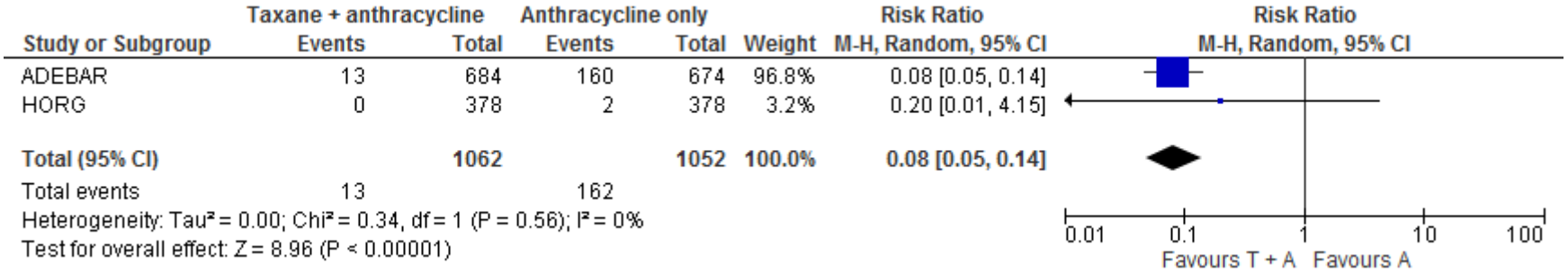


Figure 8: Treatment-related morbidity: leukopenia at 5 year follow-up

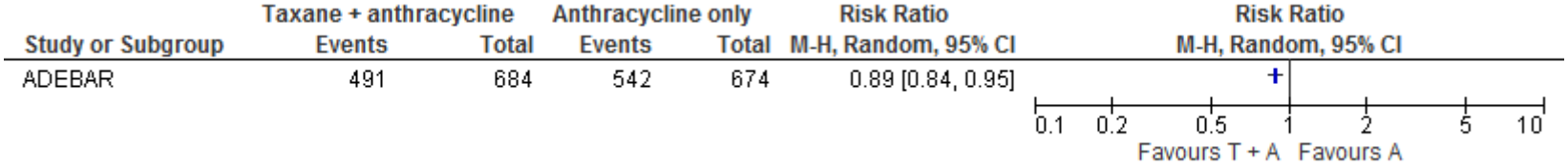


Figure 9: Treatment-related morbidity: nausea at 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADEBAR	8	684	11	674	32.2%	0.72 [0.29, 1.77]
HORG	23	378	18	378	67.8%	1.28 [0.70, 2.33]
Total (95% CI)		**1062**		**1052**	**100.0%**	**1.06 [0.62, 1.80]**
Total events	31		29			

Heterogeneity: Tau² = 0.01; Chi² = 1.09, df = 1 (P = 0.30); I² = 8%
Test for overall effect: Z = 0.22 (P = 0.83)

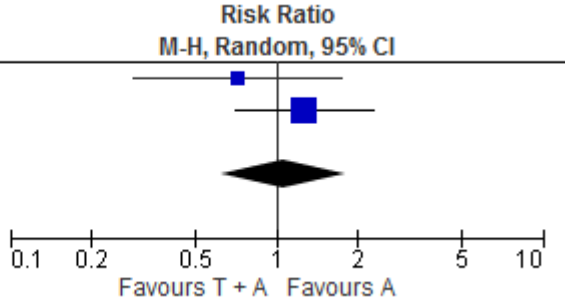


Figure 10: Treatment-related morbidity: vomiting at 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
ADEBAR	24	684	12	674	1.97 [0.99, 3.91]

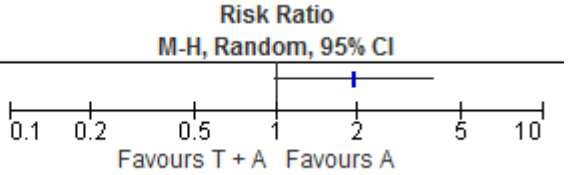


Figure 11: Treatment-related morbidity: diarrhoea at 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADEBAR	7	684	12	674	54.4%	0.57 [0.23, 1.45]
HORG	14	378	0	378	45.6%	29.00 [1.74, 484.39]
Total (95% CI)		**1062**		**1052**	**100.0%**	**3.44 [0.04, 301.37]**
Total events	21		12			

Heterogeneity: Tau² = 9.36; Chi² = 9.18, df = 1 (P = 0.002); I² = 89%
Test for overall effect: Z = 0.54 (P = 0.59)

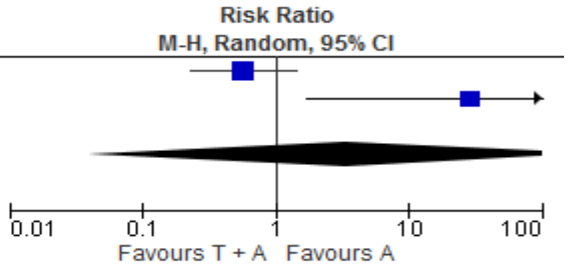


Figure 12: Treatment-related morbidity: hypersensitivity at 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADEBAR	1	684	0	674	45.4%	2.96 [0.12, 72.44]
HORG	4	378	0	378	54.6%	9.00 [0.49, 166.58]
Total (95% CI)		**1062**		**1052**	**100.0%**	**5.43 [0.63, 46.87]**
Total events	5		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)

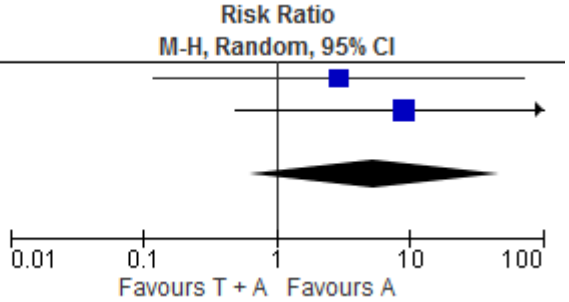


Figure 13: Treatment-related morbidity: neurological at 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
ADEBAR	5	684	1	674	4.93 [0.58, 42.06]

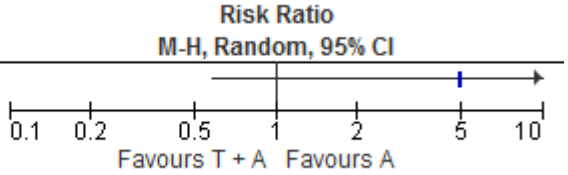


Figure 14: Treatment-related mortality at 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
HORG	0	378	2	378	0.20 [0.01, 4.15]

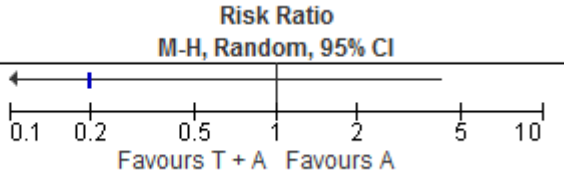


Figure 15: Adequate dose intensity: dose reductions

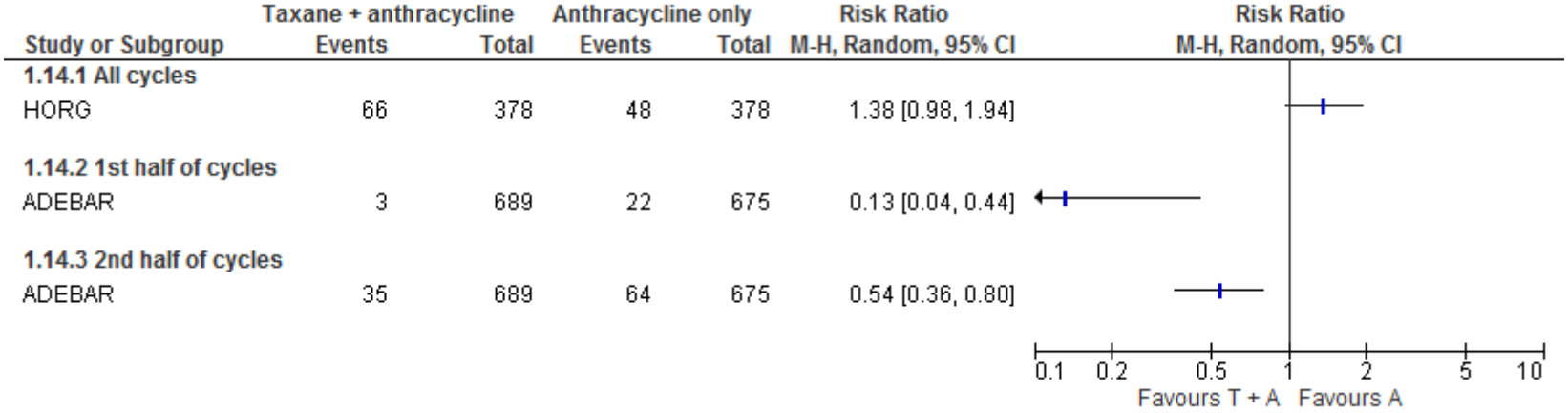


Figure 16: HRQoL: global health (measured by EORTC QLQ-30) at 5 year follow-up

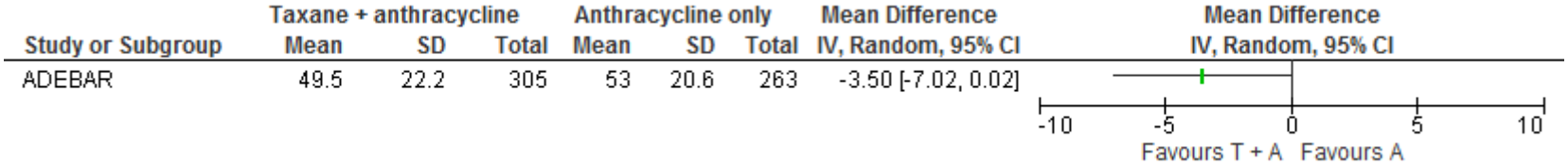


Figure 17: HRQoL: physical functioning (measured by EORTC QLQ-30) at 5 year follow-up

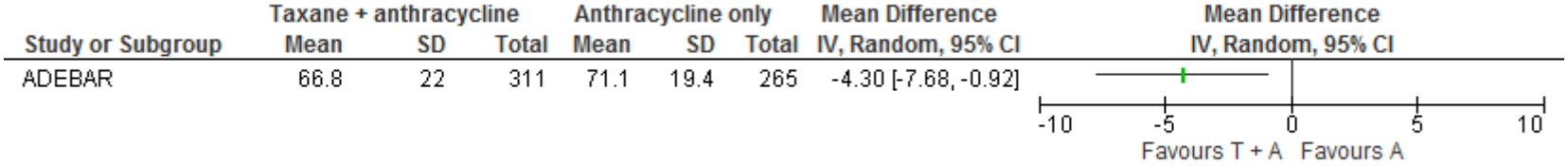


Figure 18: HRQoL: nausea and vomiting (measured by EORTC QLQ-30) at 5 year follow-up

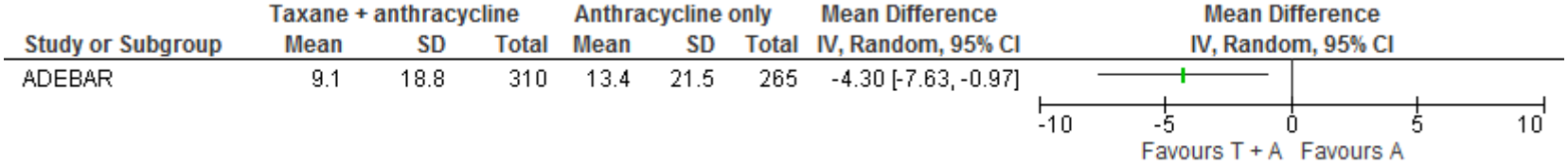


Figure 19: HRQoL: fatigue (measured by EORTC QLQ-30) at 5 year follow-up

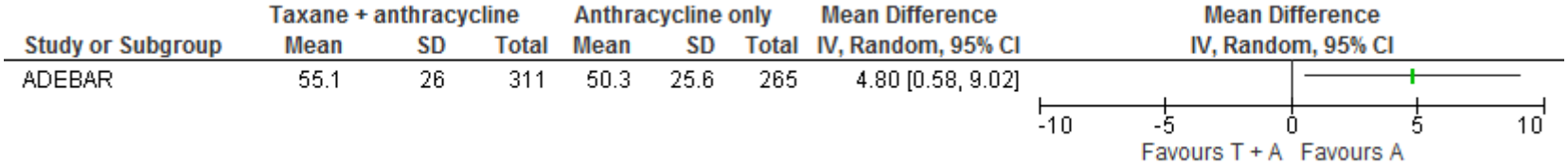
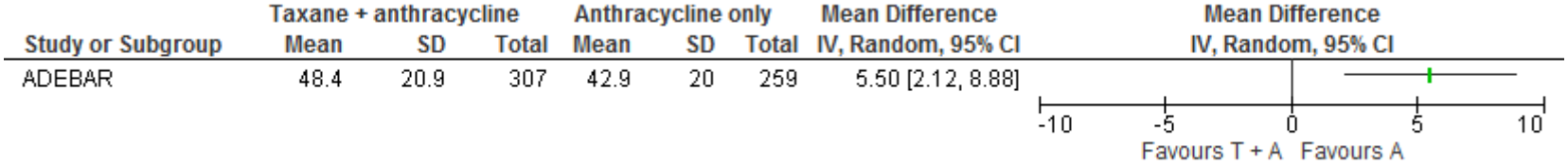
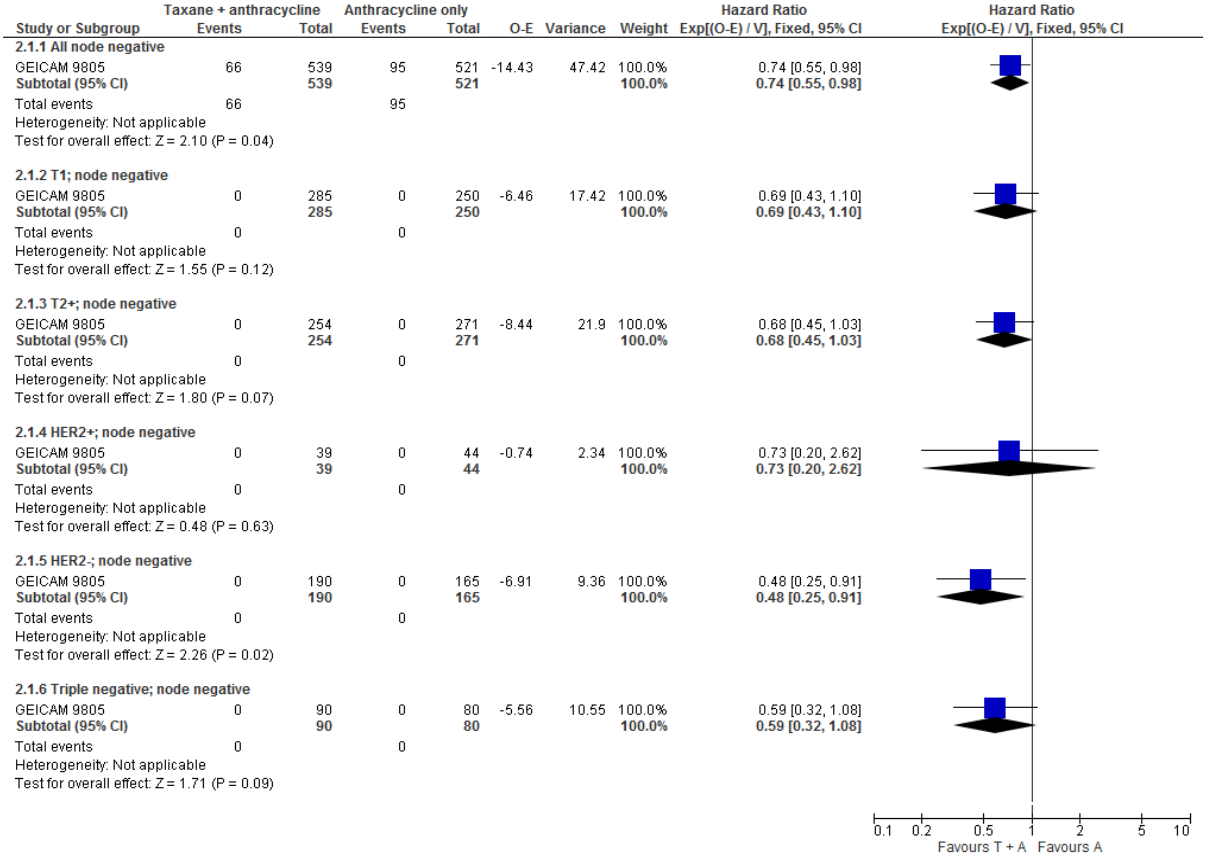


Figure 20: HRQoL: systemic therapy side effects (measured by EORTC QLQ-30) at 5 year follow-up



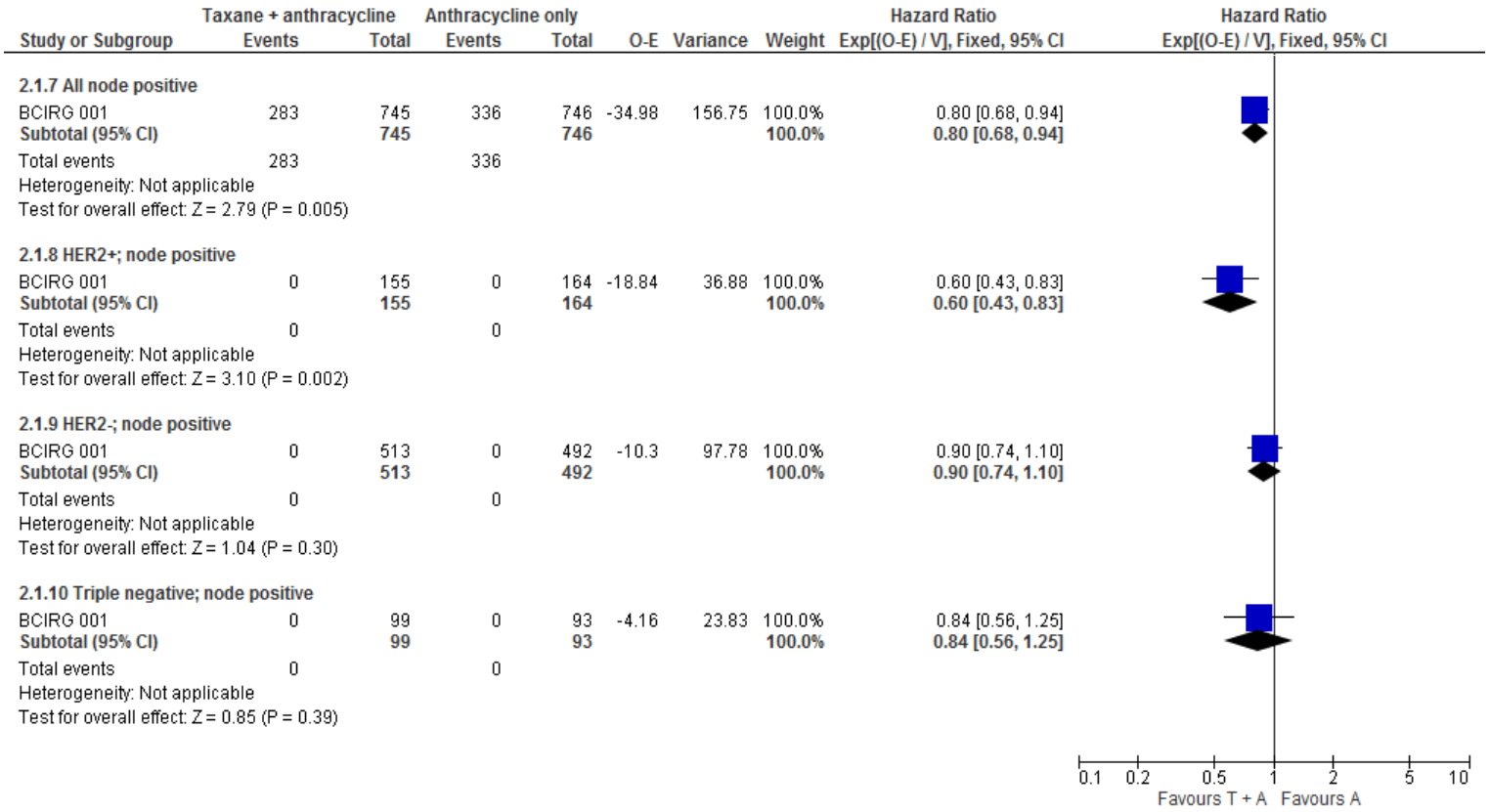
Comparison 2. TAC versus FAC

Figure 21: Disease-free survival at 6.4 year follow-up – node negative subgroups



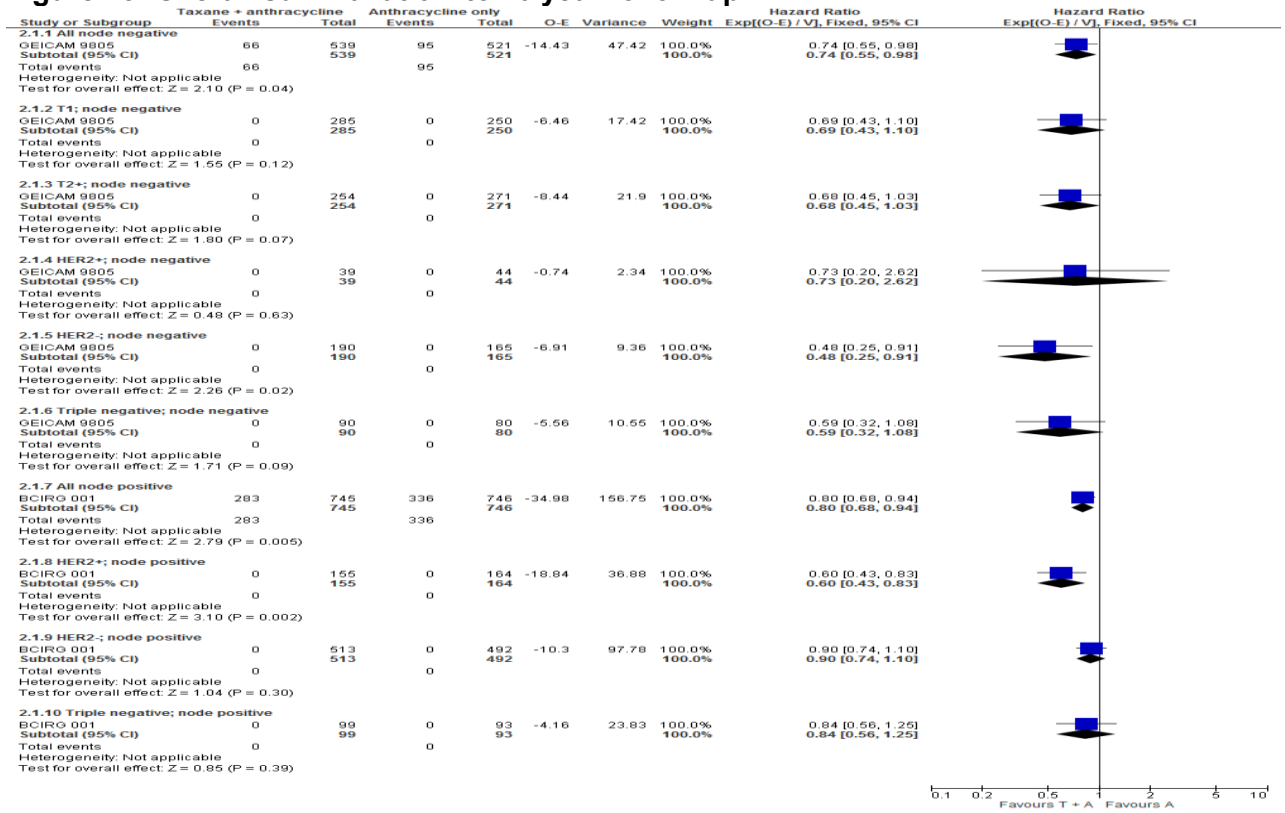
Note. Number of events in each arm not reported for subgroups based on hormone receptor

Figure 22: Disease-free survival at 10 year follow-up – node positive subgroups



Note. Number of events in each arm not reported for subgroups based on hormone receptor

Figure 23: Overall survival at 6.4 to 10 year follow-up



Note. Number of events in each arm not reported for subgroups based on hormone receptor status

Figure 24: Treatment-related morbidity: neutropenia at 6.4 year follow-up

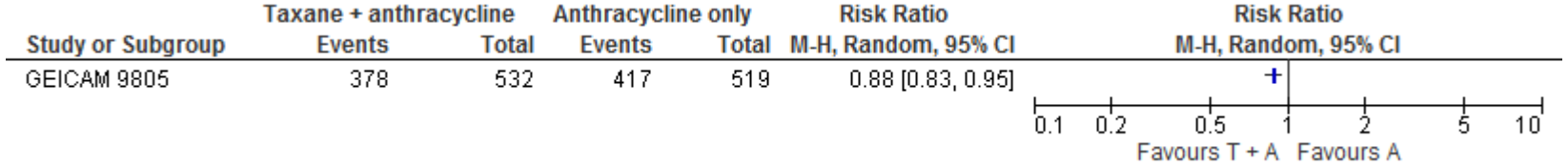


Figure 25: Treatment-related morbidity: febrile neutropenia at 6.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GEICAM 9805	51	532	12	519	4.15 [2.24, 7.69]

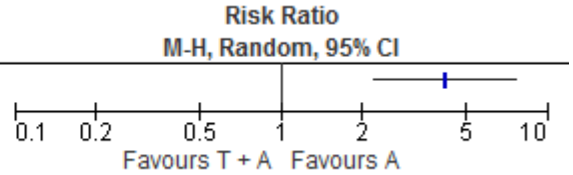


Figure 26: Treatment-related morbidity: neutropenic fever at 6.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GEICAM 9805	35	532	14	519	2.44 [1.33, 4.48]

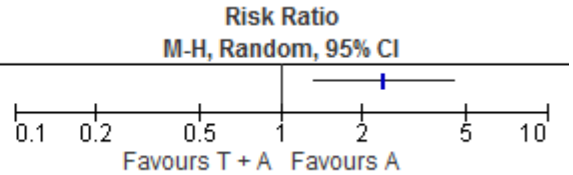


Figure 27: Treatment-related morbidity: anaemia at 6.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GEICAM 9805	504	532	360	519	1.37 [1.29, 1.45]

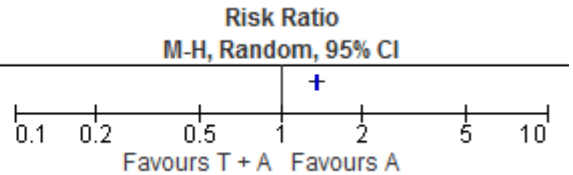


Figure 28: Treatment-related morbidity: leukopenia at 6.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GEICAM 9805	456	532	439	519	1.01 [0.96, 1.07]

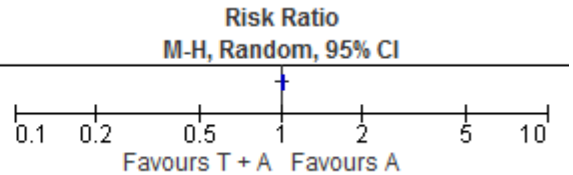


Figure 29: Treatment-related morbidity: thrombocytopenia at 6.4 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
GEICAM 9805	64	532	26	519	2.40 [1.55, 3.73]	

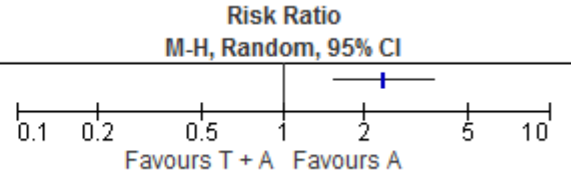


Figure 30: Treatment-related morbidity: nausea at 6.4 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
GEICAM 9805	379	532	387	519	0.96 [0.89, 1.03]	

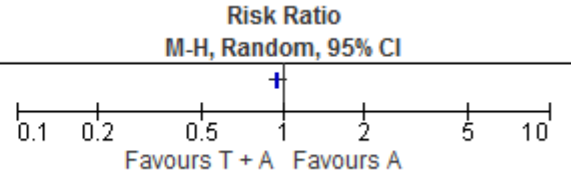


Figure 31: Treatment-related morbidity: vomiting at 6.4 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
GEICAM 9805	292	532	294	519	0.97 [0.87, 1.08]	

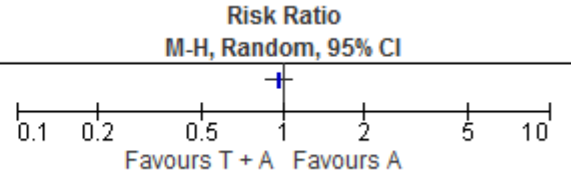


Figure 32: Treatment-related morbidity: diarrhoea at 6.4 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
GEICAM 9805	147	532	70	519	2.05 [1.58, 2.65]	

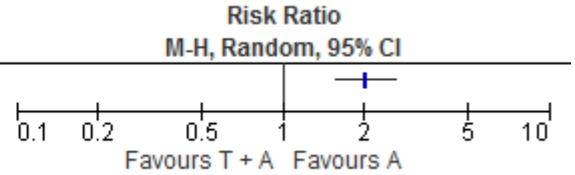


Figure 33: Treatment-related morbidity: peripheral sensory neuropathy at 6.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GEICAM 9805	83	632	38	519	1.79 [1.24, 2.59]

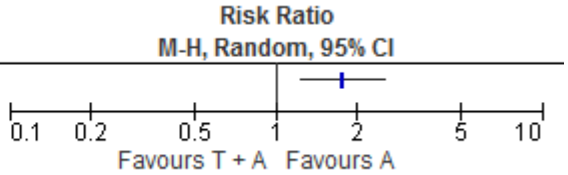


Figure 34: Treatment-related morbidity: peripheral motor neuropathy at 6.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GEICAM 9805	18	532	2	519	8.78 [2.05, 37.65]

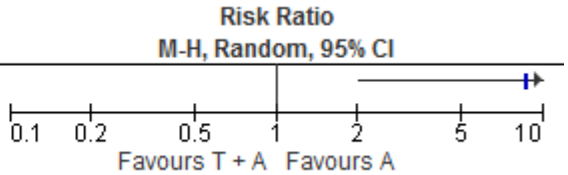


Figure 35: Treatment-related morbidity: hypersensitivity at 6.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GEICAM 9805	23	532	8	519	2.80 [1.27, 6.21]

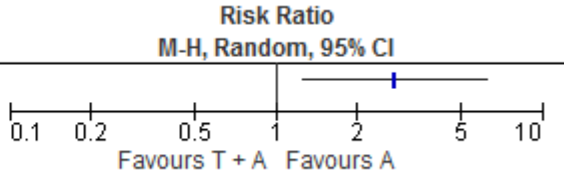


Figure 36: Treatment-related morbidity: acute myeloid leukaemia at 10.3 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
BCIRG 001	4	744	1	736	3.96 [0.44, 35.32]

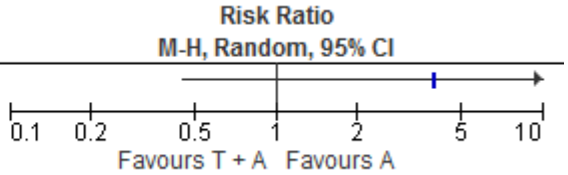


Figure 37: Treatment-related morbidity: chronic lymphocytic leukaemia at 10.3 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
BCIRG 001	0	744	1	736	0.33 [0.01, 8.08]	

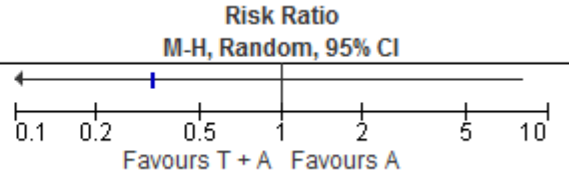
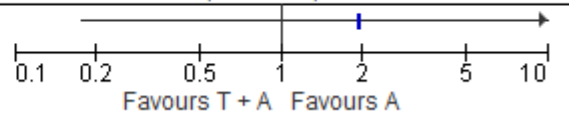


Figure 38: Treatment-related morbidity: myelodysplasia at 10.3 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
BCIRG 001	2	744	1	736	1.98 [0.18, 21.77]	



Comparison 3. FEC/FAC + docetaxel/paclitaxel versus FEC/FA

Figure 39: Disease-free survival at 5 to 10 year follow-up – mixed populations

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
3.17.1 Mixed population: direct evidence								
Albert 2011	18	257	18	249	-3.39	9.04	6.7%	0.69 [0.36, 1.32]
GEICAM 9906	159	614	205	632	-24.85	86.4	64.2%	0.75 [0.61, 0.93]
Sakr 2013	72	327	86	330	-15.54	39.13	29.1%	0.67 [0.49, 0.92]
Subtotal (95% CI)		**1198**		**1211**			**100.0%**	**0.72 [0.61, 0.86]**
Total events	249		309					
Heterogeneity: Chi² = 0.35, df = 2 (P = 0.84); I² = 0%								
Test for overall effect: Z = 3.77 (P = 0.0002)								
3.17.2 Mixed population: indirect evidence (comparison)								
TACT	517	2073	539	2089	-13.74	267.93	100.0%	0.95 [0.84, 1.07]
Subtotal (95% CI)		**2073**		**2089**			**100.0%**	**0.95 [0.84, 1.07]**
Total events	517		539					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.84 (P = 0.40)								

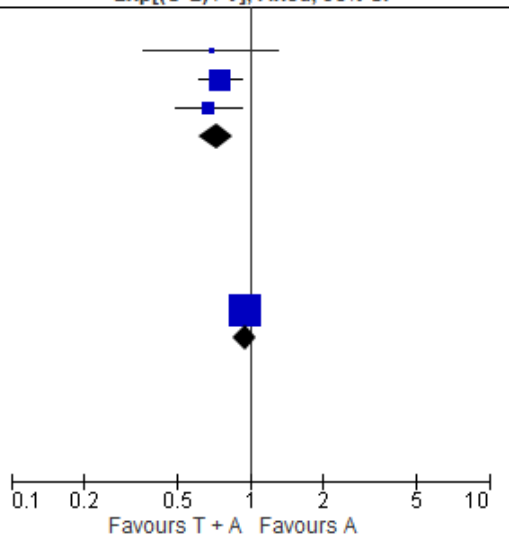
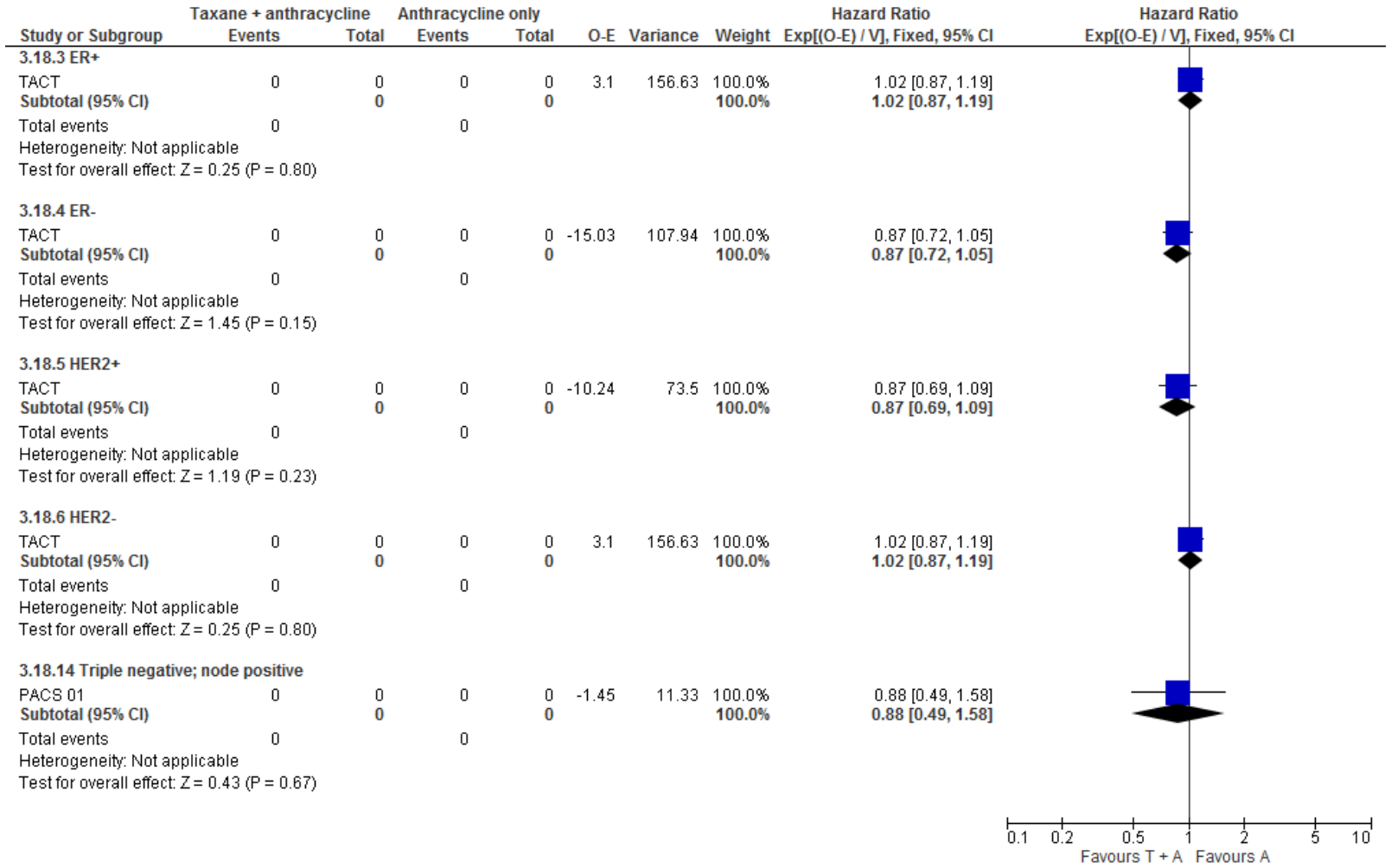


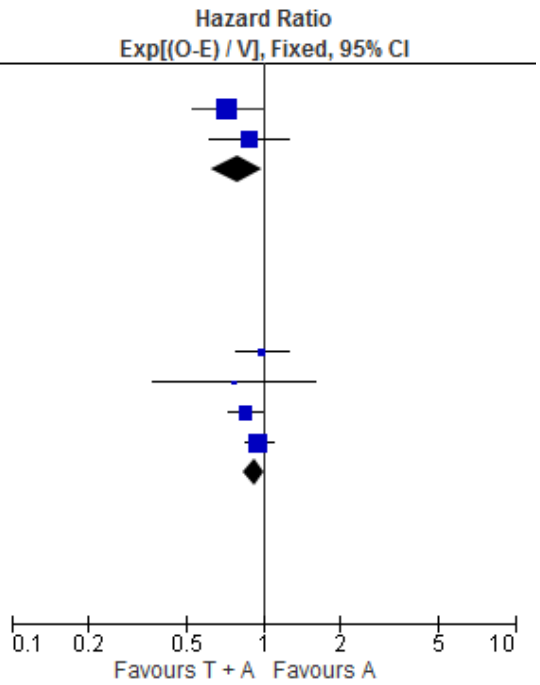
Figure 40: Disease-free survival at 5 year follow-up – hormone receptor subgroups



Note. Number of events and participants in each arm not reported in the TACT trial or the triple negative, node positive subgroup

Figure 41: Disease-free survival at 5 to 10 year follow-up – nodal status subgroups

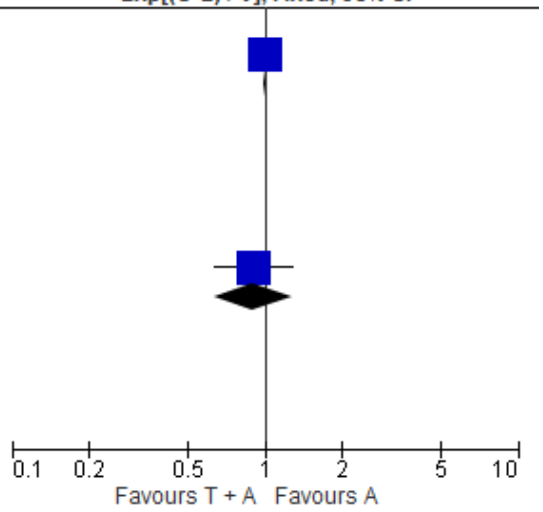
Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
3.19.7 Node negative								
GEICAM/2003-02	67	951	94	974	-12.83	39.05	56.7%	0.72 [0.53, 0.99]
TACT	0	0	0	0	-3.82	29.85	43.3%	0.88 [0.61, 1.26]
Subtotal (95% CI)		**951**		**974**			**100.0%**	**0.79 [0.62, 0.99]**
Total events	67		94					
Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%								
Test for overall effect: Z = 2.01 (P = 0.04)								
3.19.8 Node positive								
AERO-B2000	132	420	135	417	-0.64	63.36	13.6%	0.99 [0.77, 1.27]
Albert 2011	13	174	15	175	-1.84	6.96	1.5%	0.77 [0.37, 1.61]
PACS 01	301	1003	338	996	-26.9	165.55	35.4%	0.85 [0.73, 0.99]
TACT	0	0	0	0	-9.44	231.15	49.5%	0.96 [0.84, 1.09]
Subtotal (95% CI)		**1597**		**1588**			**100.0%**	**0.92 [0.84, 1.01]**
Total events	446		488					
Heterogeneity: Chi² = 2.02, df = 3 (P = 0.57); I² = 0%								
Test for overall effect: Z = 1.80 (P = 0.07)								



Note. Number of events and participants in each arm not reported in the TACT trial

Figure 42: Disease-free survival at 5 year follow-up – age subgroups

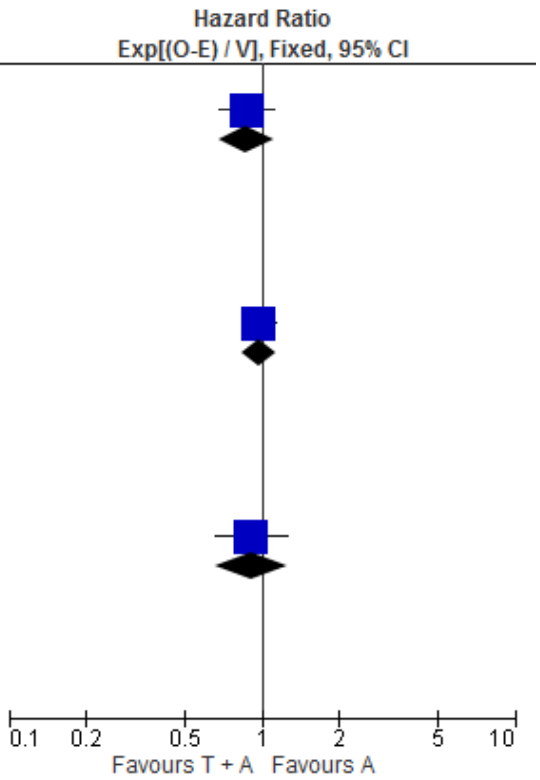
Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
3.20.9 Aged <60								
TACT	0	0	0	0	-9.44	23,115	100.0%	1.00 [0.99, 1.01]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**1.00 [0.99, 1.01]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.95)								
3.20.10 Aged 60+								
TACT	0	0	0	0	-3.15	29.92	100.0%	0.90 [0.63, 1.29]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**0.90 [0.63, 1.29]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.58 (P = 0.56)								



Note. Number of events and participants in each arm not reported in the TACT trial

Figure 43: Disease-free survival at 5 year follow-up – tumour size subgroups

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
3.21.11 T1								
TACT	0	0	0	0	-8.91	63.99	100.0%	0.87 [0.68, 1.11]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**0.87 [0.68, 1.11]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								
3.21.12 T2								
TACT	0	0	0	0	-5.02	164.77	100.0%	0.97 [0.83, 1.13]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**0.97 [0.83, 1.13]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.39 (P = 0.70)								
3.21.13 T3/4								
TACT	0	0	0	0	-3.47	36.75	100.0%	0.91 [0.66, 1.26]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**0.91 [0.66, 1.26]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.57 (P = 0.57)								



Note. Number of events and participants in each arm not reported in the TACT trial

Figure 44: Overall survival at 5 to 10 year follow-up – mixed populations and nodal status subgroups

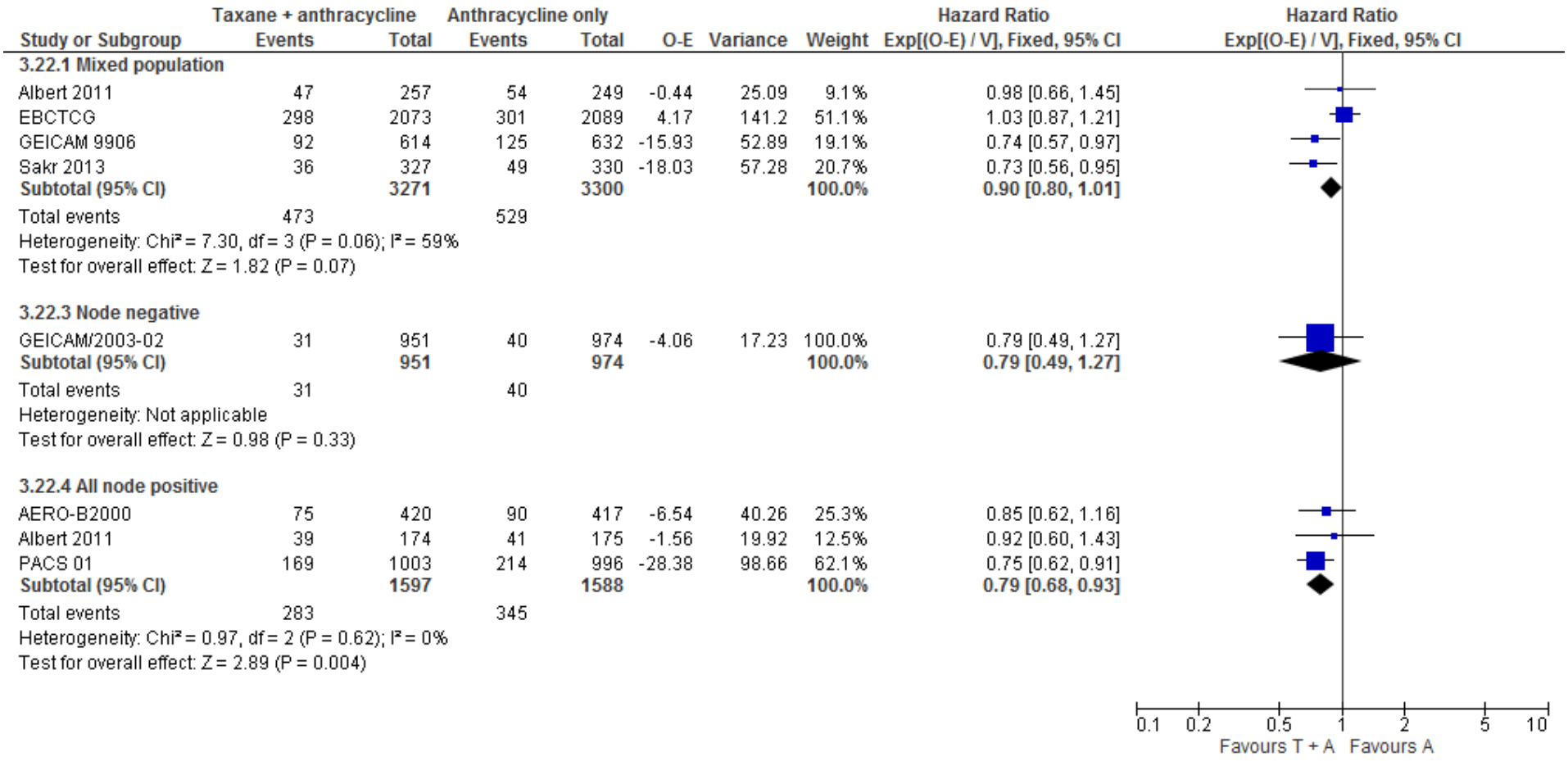


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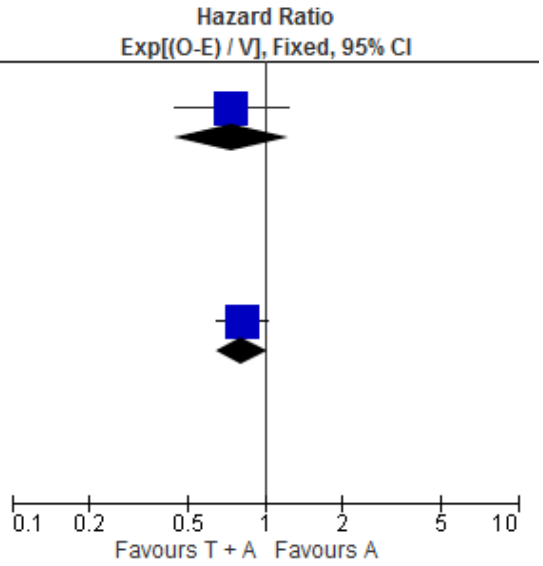
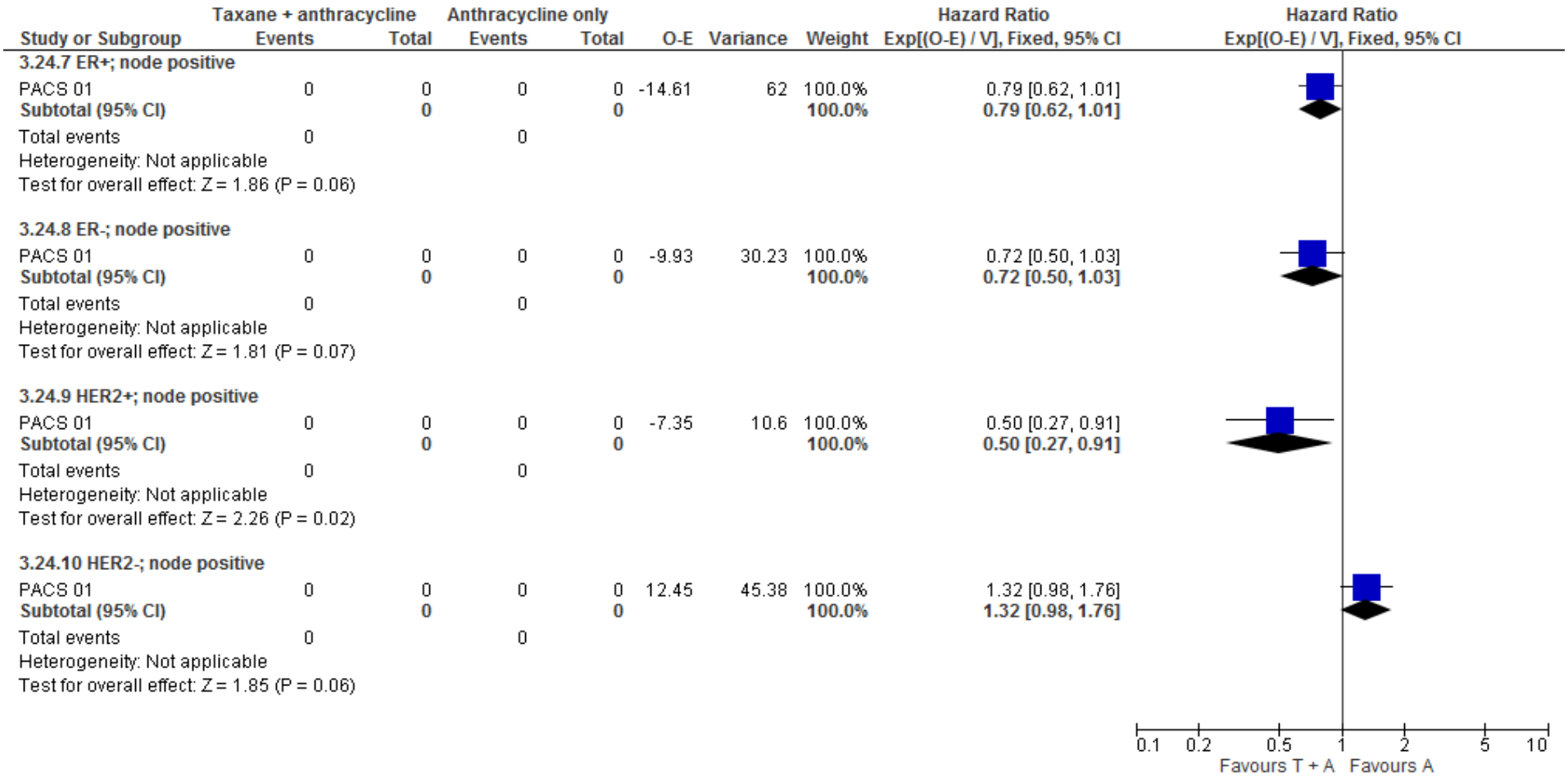
Figure 45: Overall survival at 5 year follow-up – tumour size subgroups

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
3.23.5 T stage 1; node positive								
PACS 01	0	0	0	0	-4.38	14.54	100.0%	0.74 [0.44, 1.24]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**0.74 [0.44, 1.24]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.15 (P = 0.25)								
3.23.6 T stage 2+; node positive								
PACS 01	0	0	0	0	-14.3	67.86	100.0%	0.81 [0.64, 1.03]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**0.81 [0.64, 1.03]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.74 (P = 0.08)								



Note. Number of events and participants in each arm not reported

Figure 46: Overall survival at 5 year follow-up – hormone receptor status subgroups



Note. Number of events and participants in each arm not reported

Figure 47: Treatment-related morbidity: neutropenia at 5 to 9 year follow-up

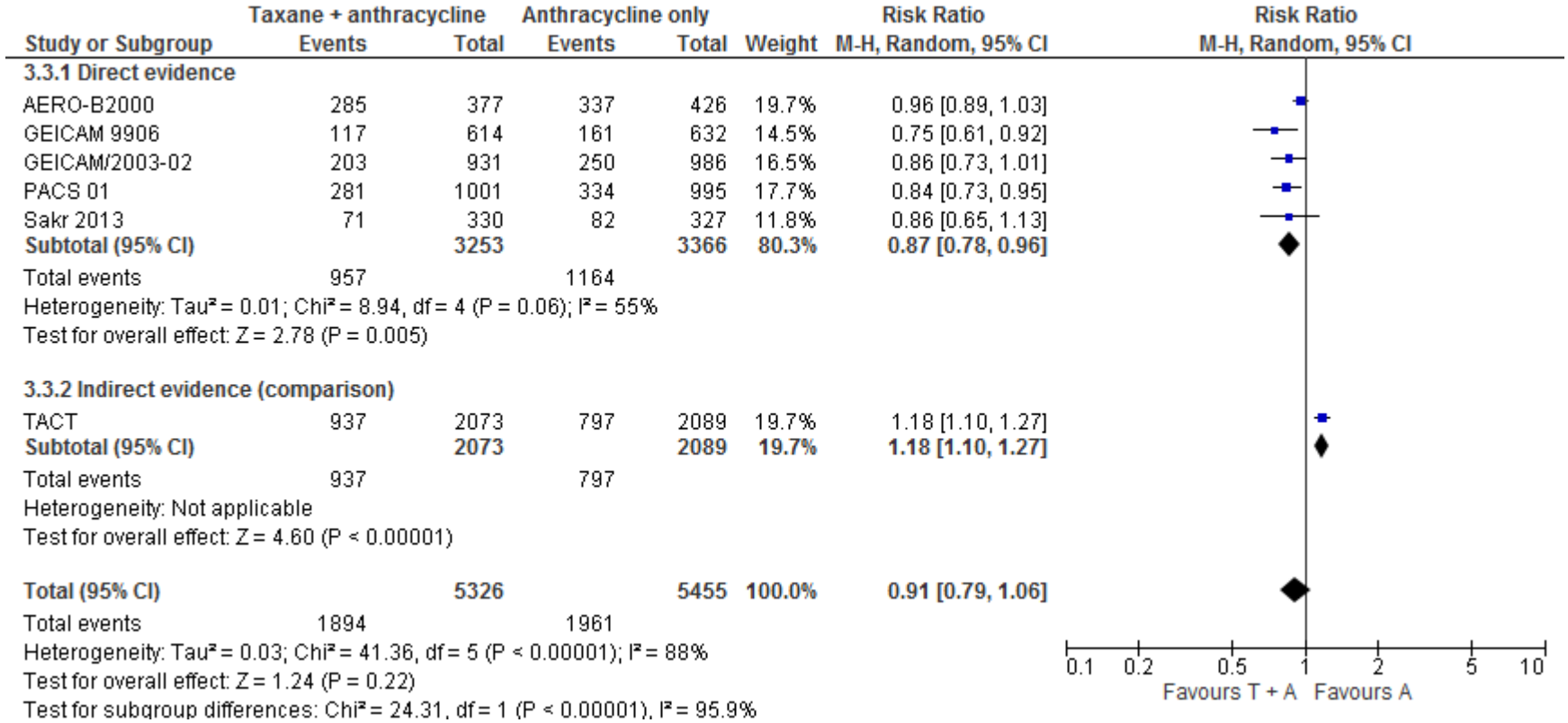


Figure 48: Treatment-related morbidity: febrile neutropenia at 5 to 9 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Direct evidence						
AERO-B2000	30	377	33	426	19.1%	1.03 [0.64, 1.65]
GEICAM 9906	31	614	60	632	19.8%	0.53 [0.35, 0.81]
PACS 01	112	1001	84	995	21.6%	1.33 [1.01, 1.73]
Sakr 2013	27	330	22	327	18.1%	1.22 [0.71, 2.09]
Subtotal (95% CI)		**2322**		**2380**	**78.6%**	**0.97 [0.63, 1.50]**
Total events	200		199			
Heterogeneity: Tau² = 0.15; Chi² = 13.30, df = 3 (P = 0.004); I² = 77%						
Test for overall effect: Z = 0.13 (P = 0.90)						
3.4.2 Indirect evidence (comparison)						
TACT	146	2073	61	2089	21.4%	2.41 [1.80, 3.23]
Subtotal (95% CI)		**2073**		**2089**	**21.4%**	**2.41 [1.80, 3.23]**
Total events	146		61			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.90 (P < 0.00001)						
Total (95% CI)		**4395**		**4469**	**100.0%**	**1.18 [0.71, 1.94]**
Total events	346		260			
Heterogeneity: Tau² = 0.28; Chi² = 35.54, df = 4 (P < 0.00001); I² = 89%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi² = 11.57, df = 1 (P = 0.0007), I² = 91.4%						

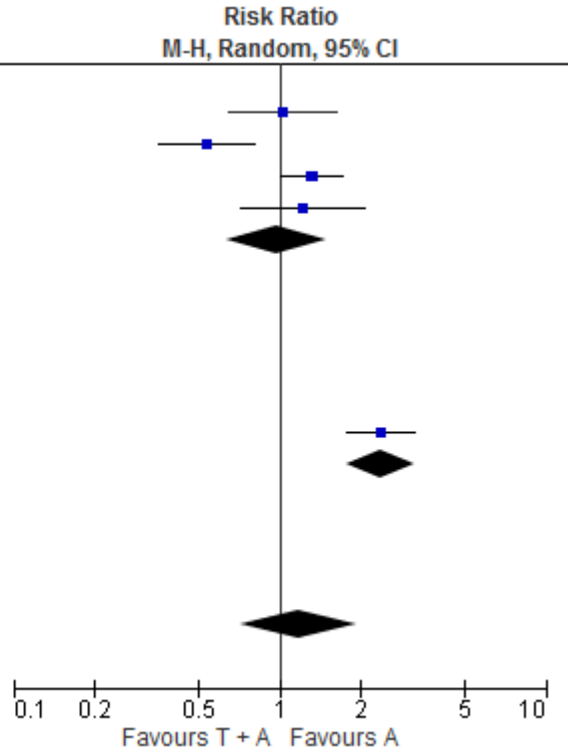


Figure 49: Treatment-related morbidity: anaemia at 5 to 8 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
PACS 01	7	1001	14	995	36.7%	0.50 [0.20, 1.23]
Sakr 2013	2	330	4	327	10.5%	0.50 [0.09, 2.69]
TACT	13	2073	14	2089	52.8%	0.94 [0.44, 1.99]
Total (95% CI)		**3404**		**3411**	**100.0%**	**0.69 [0.40, 1.20]**
Total events	22		32			

Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)

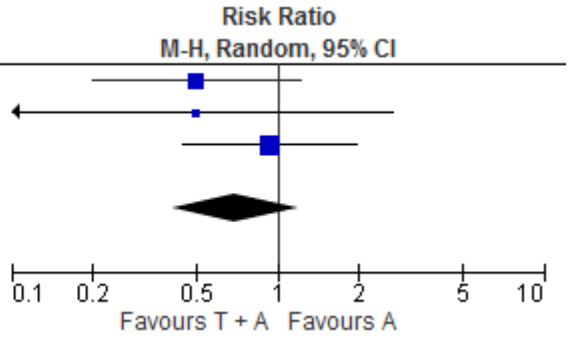


Figure 50: Treatment-related morbidity: thrombocytopenia at 5 to 9 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AERO-B2000	76	377	88	426	55.9%	0.98 [0.74, 1.28]
PACS 01	4	1001	3	995	9.1%	1.33 [0.30, 5.91]
Sakr 2013	2	330	2	327	5.7%	0.99 [0.14, 6.99]
TACT	12	2073	27	2089	29.3%	0.45 [0.23, 0.88]
Total (95% CI)		**3781**		**3837**	**100.0%**	**0.80 [0.49, 1.30]**
Total events	94		120			

Heterogeneity: Tau² = 0.09; Chi² = 4.72, df = 3 (P = 0.19); I² = 36%
Test for overall effect: Z = 0.90 (P = 0.37)

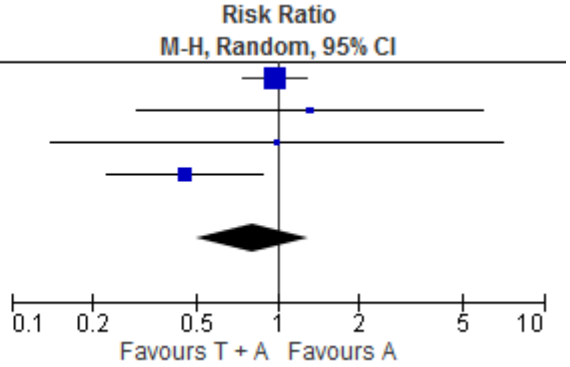


Figure 51: Treatment-related morbidity: leukopenia at 5 to 9 year follow-up

	Taxane + anthracycline		Anthracycline only			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
AERO-B2000	26	377	29	426	24.0%	1.01 [0.61, 1.69]
GEICAM/2003-02	78	931	93	986	76.0%	0.89 [0.67, 1.18]
Total (95% CI)		**1308**		**1412**	**100.0%**	**0.92 [0.71, 1.18]**
Total events	104		122			

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.50)

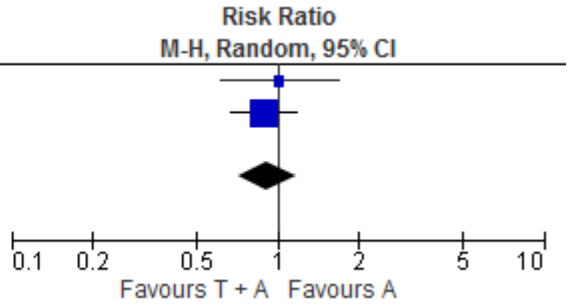


Figure 52: Treatment-related morbidity: lymphopenia at 5 year follow-up

	Taxane + anthracycline		Anthracycline only			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
GEICAM/2003-02	9	931	10	986		0.95 [0.39, 2.34]

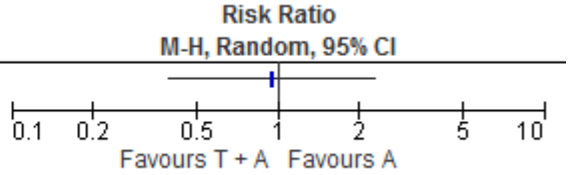


Figure 53: Treatment-related morbidity: vomiting at 5 to 9 year follow-up

	Taxane + anthracycline		Anthracycline only			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
AERO-B2000	163	377	206	426	77.1%	0.89 [0.77, 1.04]
GEICAM 9906	45	614	63	632	13.2%	0.74 [0.51, 1.06]
GEICAM/2003-02	40	931	40	986	9.6%	1.06 [0.69, 1.63]
Total (95% CI)		**1922**		**2044**	**100.0%**	**0.89 [0.78, 1.01]**
Total events	248		309			

Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)

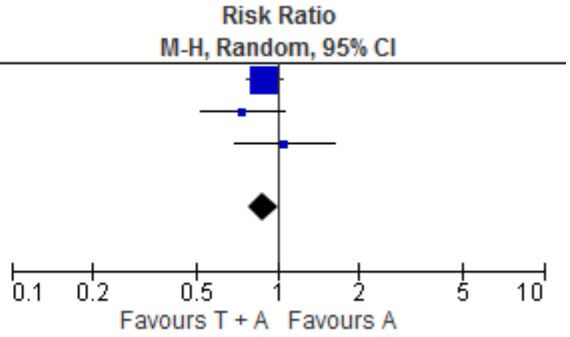


Figure 54: Treatment-related morbidity: nausea at 5 to 9 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AERO-B2000	293	377	349	426	96.2%	0.95 [0.88, 1.02]
GEICAM 9906	33	614	37	632	2.3%	0.92 [0.58, 1.45]
GEICAM/2003-02	25	931	25	986	1.6%	1.06 [0.61, 1.83]
Total (95% CI)		**1922**		**2044**	**100.0%**	**0.95 [0.89, 1.02]**
Total events	351		411			

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)

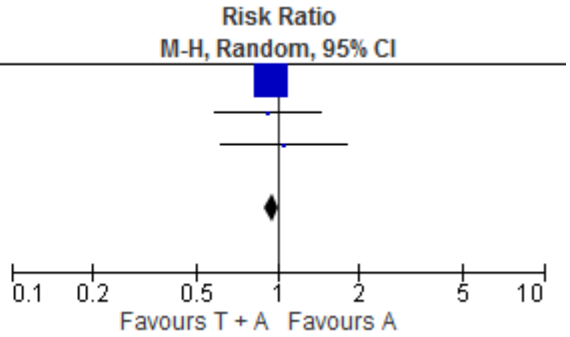


Figure 55: Treatment-related morbidity: nausea/vomiting at 5 to 8 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.11.1 Direct evidence						
PACS 01	112	1001	204	995	34.9%	0.55 [0.44, 0.68]
Sakr 2013	37	330	62	327	29.3%	0.59 [0.41, 0.86]
Subtotal (95% CI)		**1331**		**1322**	**64.3%**	**0.56 [0.46, 0.67]**
Total events	149		266			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 6.19 (P < 0.00001)						
3.11.2 Indirect evidence (comparison)						
TACT	199	2073	205	2089	35.7%	0.98 [0.81, 1.18]
Subtotal (95% CI)		**2073**		**2089**	**35.7%**	**0.98 [0.81, 1.18]**
Total events	199		205			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
Total (95% CI)		**3404**		**3411**	**100.0%**	**0.69 [0.45, 1.05]**
Total events	348		471			
Heterogeneity: Tau² = 0.12; Chi² = 17.91, df = 2 (P = 0.0001); I² = 89%						
Test for overall effect: Z = 1.74 (P = 0.08)						
Test for subgroup differences: Chi² = 17.78, df = 1 (P < 0.0001), I² = 94.4%						

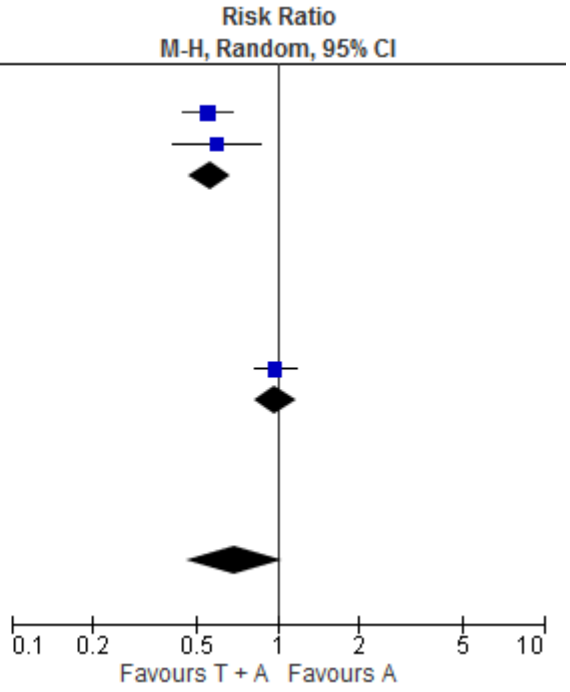


Figure 56: Treatment-related morbidity: diarrhoea at 5 to 9 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AERO-B2000	15	377	21	426	33.2%	0.81 [0.42, 1.54]
TACT	77	2073	59	2089	66.8%	1.32 [0.94, 1.84]
Total (95% CI)		**2450**		**2515**	**100.0%**	**1.12 [0.71, 1.76]**
Total events	92		80			
Heterogeneity: Tau² = 0.05; Chi² = 1.72, df = 1 (P = 0.19); I² = 42%						
Test for overall effect: Z = 0.49 (P = 0.63)						

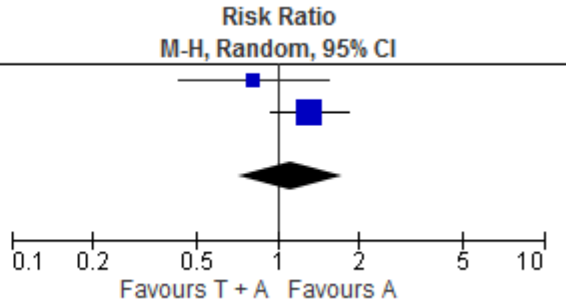


Figure 57: Treatment-related morbidity: lethargy at 5 to 9 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.13.1 Direct evidence						
AERO-B2000	6	377	9	426	14.2%	0.75 [0.27, 2.10]
GEICAM 9906	15	614	26	632	22.7%	0.59 [0.32, 1.11]
GEICAM/2003-02	74	931	34	986	28.8%	2.31 [1.55, 3.43]
Subtotal (95% CI)		**1922**		**2044**	**65.7%**	**1.06 [0.39, 2.87]**
Total events	95		69			
Heterogeneity: Tau² = 0.66; Chi² = 14.65, df = 2 (P = 0.0007); I² = 86%						
Test for overall effect: Z = 0.11 (P = 0.92)						
3.13.2 Indirect evidence (comparison)						
TACT	456	2073	272	2089	34.3%	1.69 [1.47, 1.94]
Subtotal (95% CI)		**2073**		**2089**	**34.3%**	**1.69 [1.47, 1.94]**
Total events	456		272			
Heterogeneity: Not applicable						
Test for overall effect: Z = 7.48 (P < 0.00001)						
Total (95% CI)		**3995**		**4133**	**100.0%**	**1.30 [0.79, 2.14]**
Total events	551		341			
Heterogeneity: Tau² = 0.18; Chi² = 15.36, df = 3 (P = 0.002); I² = 80%						
Test for overall effect: Z = 1.03 (P = 0.30)						
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%						

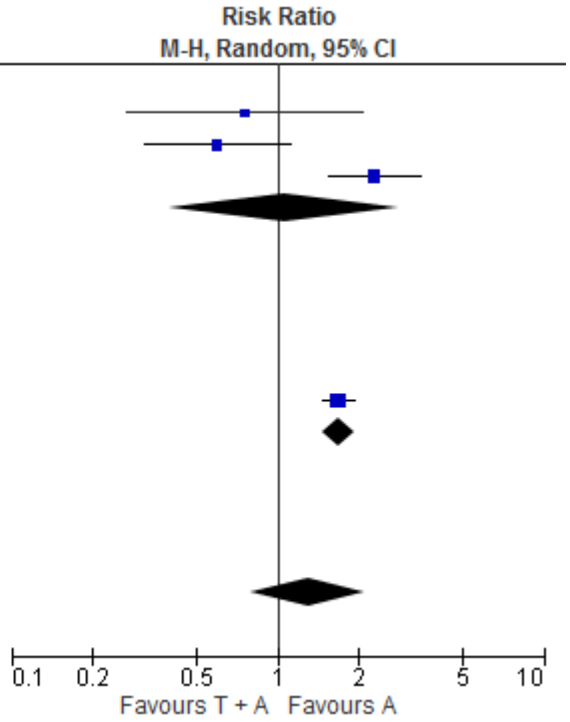


Figure 58: Treatment-related morbidity: neuropathy at 5 to 9 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.14.1 Direct evidence						
AERO-B2000	209	377	18	426	39.9%	13.12 [8.27, 20.81]
GEICAM 9906	159	614	0	632	11.2%	328.34 [20.49, 5260.44]
GEICAM/2003-02	51	931	0	986	11.1%	109.08 [6.74, 1764.91]
Subtotal (95% CI)		**1922**		**2044**	**62.3%**	**63.34 [3.83, 1048.53]**
Total events	419		18			
Heterogeneity: Tau² = 4.94; Chi² = 11.45, df = 2 (P = 0.003); I² = 83%						
Test for overall effect: Z = 2.90 (P = 0.004)						
3.14.2 Indirect evidence (comparison)						
TACT	98	2073	11	2089	37.7%	8.98 [4.83, 16.69]
Subtotal (95% CI)		**2073**		**2089**	**37.7%**	**8.98 [4.83, 16.69]**
Total events	98		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.94 (P < 0.00001)						
Total (95% CI)		**3995**		**4133**	**100.0%**	**20.65 [7.02, 60.74]**
Total events	517		29			
Heterogeneity: Tau² = 0.70; Chi² = 13.10, df = 3 (P = 0.004); I² = 77%						
Test for overall effect: Z = 5.50 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.77, df = 1 (P = 0.18), I² = 43.7%						

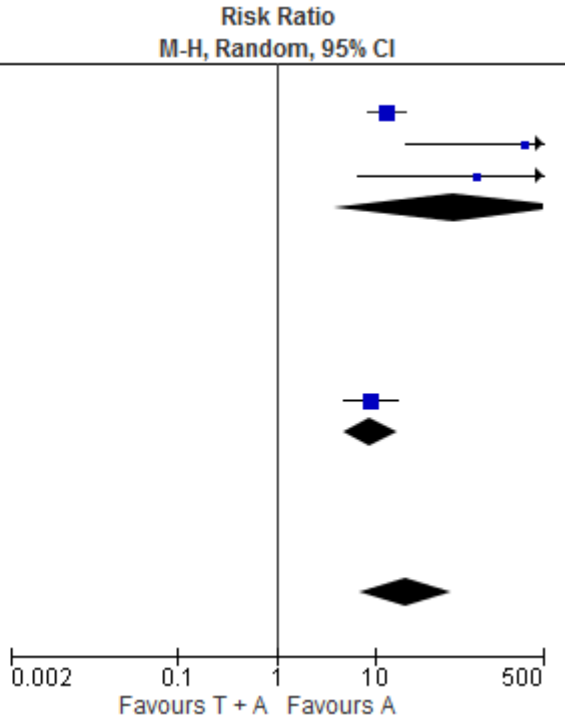


Figure 59: Treatment-related mortality at 5 year follow-up

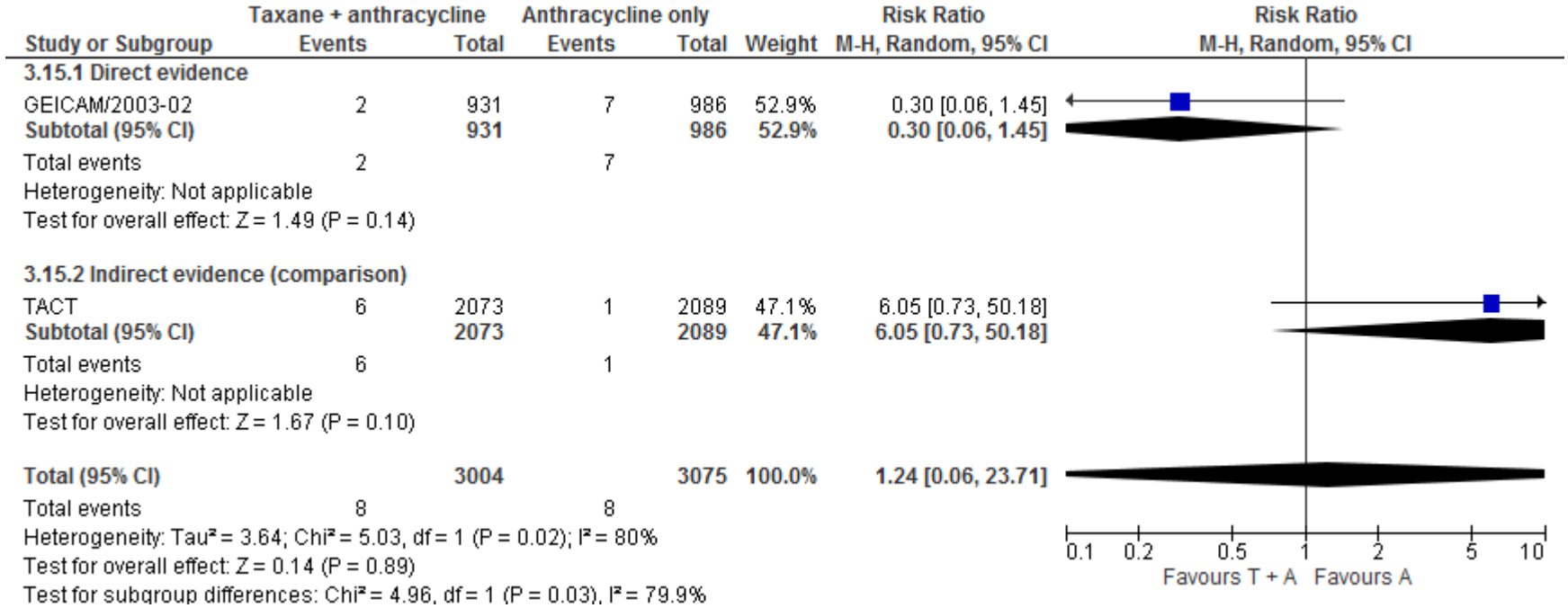
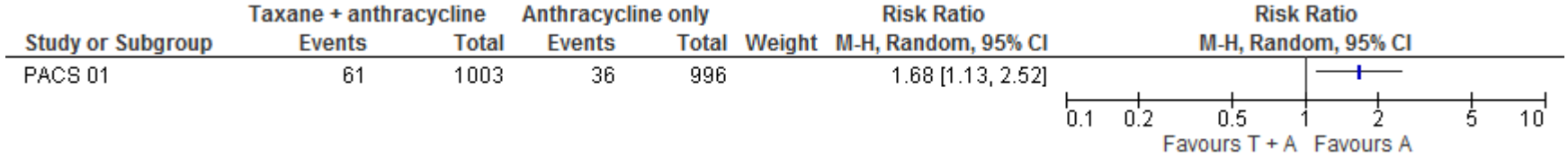


Figure 60: Adequate dose intensity: dose reductions (all cycles)



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Comparison 4. AC/EC + paclitaxel/docetaxel versus AC/EC

Figure 61: Disease-free survival at 2 to 5.8 year follow-up – mixed node positive population

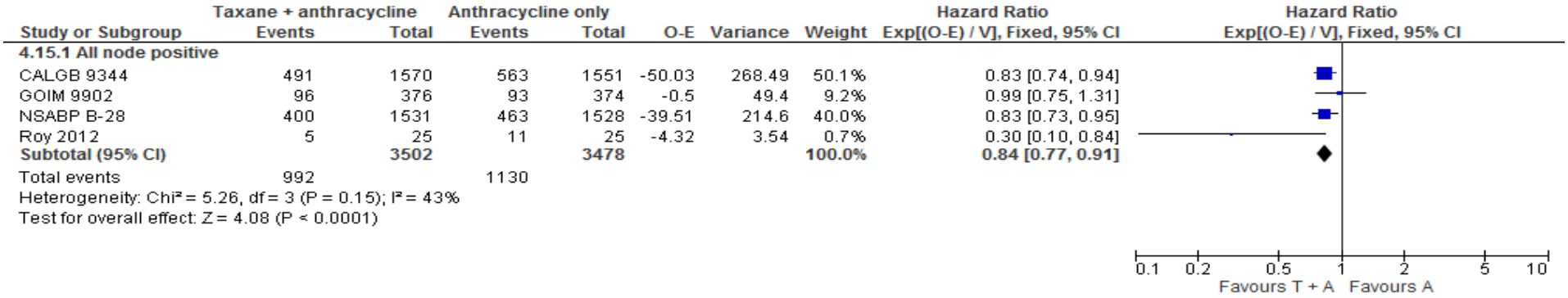
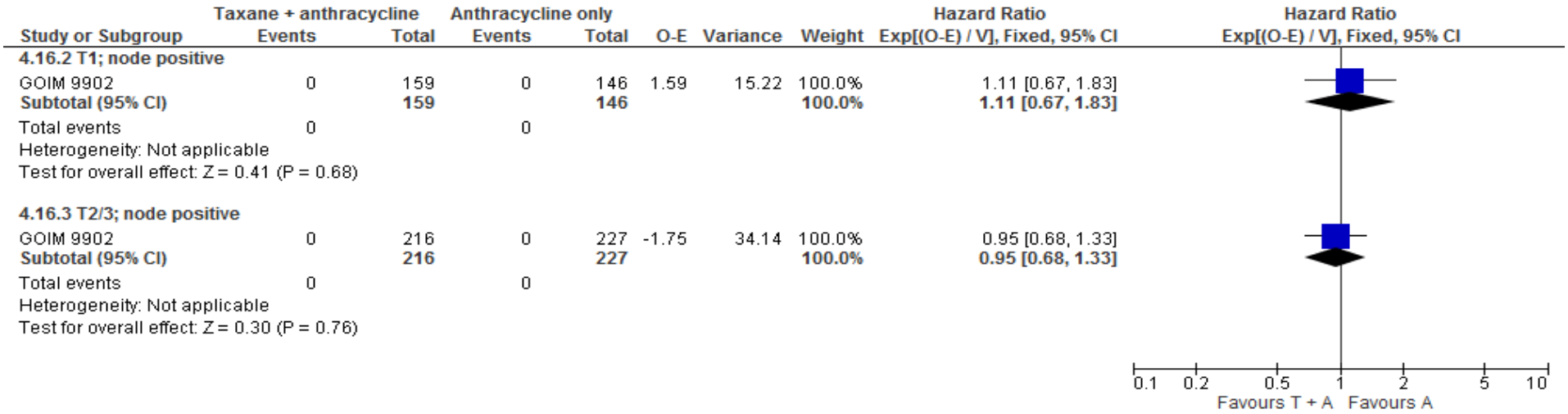


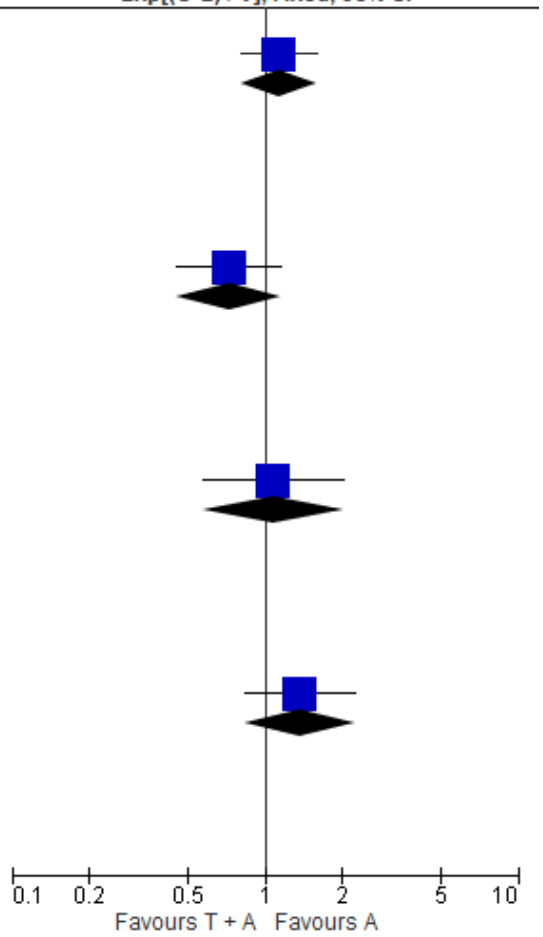
Figure 62: Disease-free survival at 5.3 year follow-up – tumour size subgroups



Note. Number of events in each arm not reported

Figure 63: Disease-free survival at 5.3 year follow-up – hormone receptor subgroups

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
4.17.4 ER+; node positive								
GOIM 9902	0	0	0	0	4.12	31.41	100.0%	1.14 [0.80, 1.62]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**1.14 [0.80, 1.62]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
4.17.5 ER-; node positive								
GOIM 9902	0	0	0	0	-5.73	17.45	100.0%	0.72 [0.45, 1.15]
Subtotal (95% CI)		**0**		**0**			**100.0%**	**0.72 [0.45, 1.15]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.37 (P = 0.17)								
4.17.6 HER2+; node positive								
GOIM 9902	0	45	0	49	0.72	9.31	100.0%	1.08 [0.57, 2.05]
Subtotal (95% CI)		**45**		**49**			**100.0%**	**1.08 [0.57, 2.05]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								
4.17.7 HER2-; node positive								
GOIM 9902	0	120	0	118	4.81	14.92	100.0%	1.38 [0.83, 2.29]
Subtotal (95% CI)		**120**		**118**			**100.0%**	**1.38 [0.83, 2.29]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								



Note. Number of events (and participants) in each arm not reported

Figure 64: Overall survival at 2 to 5.8 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
4.2.1 Mixed population								
EBCTCG	853	3121	948	3109	-59.61	395.26	99.2%	0.86 [0.78, 0.95]
Roy 2012	4	25	10	25	-3.79	3.21	0.8%	0.31 [0.10, 0.92]
Subtotal (95% CI)		**3146**		**3134**			**100.0%**	**0.85 [0.77, 0.94]**
Total events	857		958					
Heterogeneity: Chi² = 3.38, df = 1 (P = 0.07); I² = 70%								
Test for overall effect: Z = 3.18 (P = 0.001)								
4.2.2 Node positive								
GOIM 9902	39	376	43	374	-3.41	19.56	100.0%	0.84 [0.54, 1.31]
Subtotal (95% CI)		**376**		**374**			**100.0%**	**0.84 [0.54, 1.31]**
Total events	39		43					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.77 (P = 0.44)								

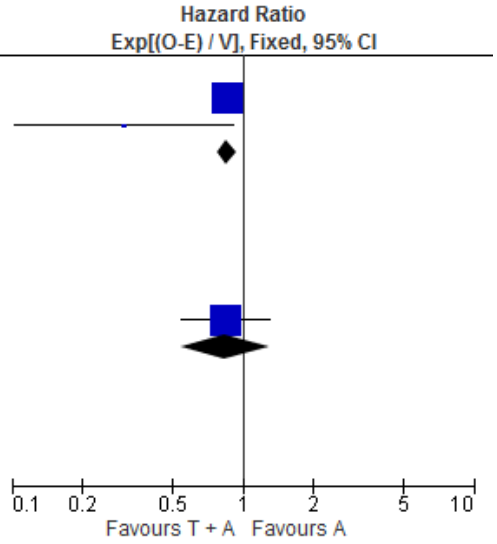


Figure 65: Treatment-related morbidity: nausea at 2 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
Roy 2012	19	25	15	25	1.27 [0.86, 1.87]

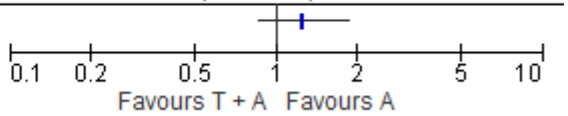


Figure 66: Treatment-related morbidity: vomiting at 2 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
Roy 2012	23	25	24	25	0.96 [0.83, 1.10]

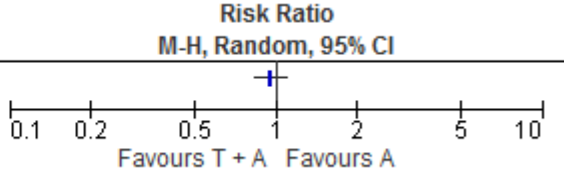


Figure 67: Treatment-related morbidity: nausea/vomiting at 5.3 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GOIM 9902	21	363	21	354	0.98 [0.54, 1.75]

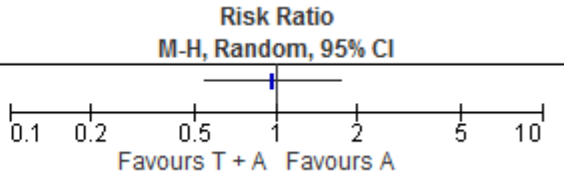


Figure 68: Treatment-related morbidity: diarrhoea at 2 to 5.3 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 AC + paclitaxel vs. AC						
Roy 2012	16	25	8	25	62.0%	2.00 [1.05, 3.80]
Subtotal (95% CI)		**25**		**25**	**62.0%**	**2.00 [1.05, 3.80]**
Total events	16		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.11 (P = 0.03)						
4.6.2 EC + docetaxel vs. EC						
GOIM 9902	12	363	1	354	38.0%	11.70 [1.53, 89.53]
Subtotal (95% CI)		**363**		**354**	**38.0%**	**11.70 [1.53, 89.53]**
Total events	12		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.37 (P = 0.02)						
Total (95% CI)		**388**		**379**	**100.0%**	**3.91 [0.58, 26.45]**
Total events	28		9			
Heterogeneity: Tau² = 1.43; Chi² = 3.41, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Chi² = 2.63, df = 1 (P = 0.10), I² = 62.0%						

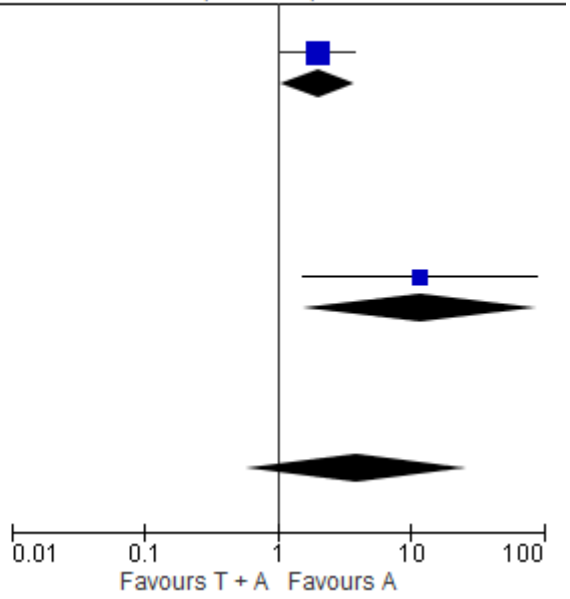


Figure 69: Treatment-related morbidity: anaemia at 2 to 5.3 year follow-up

	Taxane + anthracycline		Anthracycline only			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
GOIM 9902	7	363	9	354	25.9%	0.76 [0.29, 2.01]
Roy 2012	9	25	18	25	74.1%	0.50 [0.28, 0.89]
Total (95% CI)		**388**		**379**	**100.0%**	**0.56 [0.34, 0.92]**
Total events	16		27			

Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)

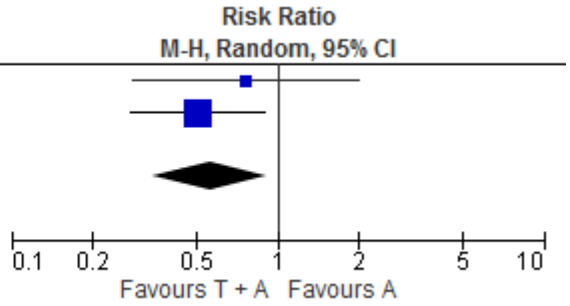


Figure 70: Treatment-related morbidity: leukopenia at 2 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI
Roy 2012	9	25	12	25	0.75 [0.39, 1.46]

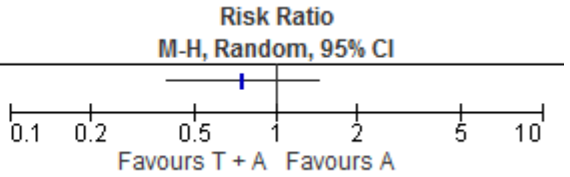


Figure 71: Treatment-related morbidity: thrombocytopenia at 2 to 5.3 year follow-up

	Taxane + anthracycline		Anthracycline only			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
GOIM 9902	4	363	2	354	100.0%	1.95 [0.36, 10.58]
Roy 2012	0	25	0	25		Not estimable
Total (95% CI)		**388**		**379**	**100.0%**	**1.95 [0.36, 10.58]**
Total events	4		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)

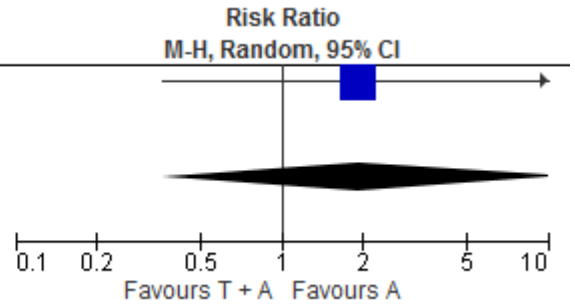


Figure 72: Treatment-related morbidity: neurotoxicity at 2 to 5.3 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
GOIM 9902	12	363	0	354	51.6%	24.38 [1.45, 410.25]
Roy 2012	3	25	0	25	48.4%	7.00 [0.38, 128.87]
Total (95% CI)		**388**		**379**	**100.0%**	**13.32 [1.75, 101.15]**
Total events	15		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)

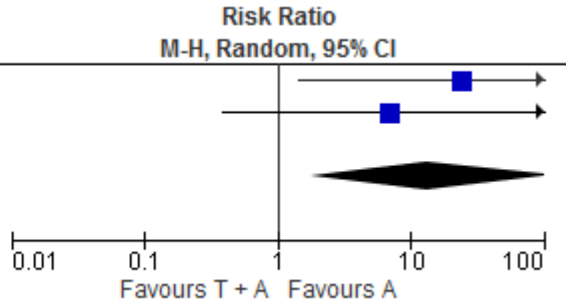


Figure 73: Treatment-related morbidity: neutropenia at 5.3 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GOIM 9902	233	363	192	354	1.18 [1.05, 1.34]

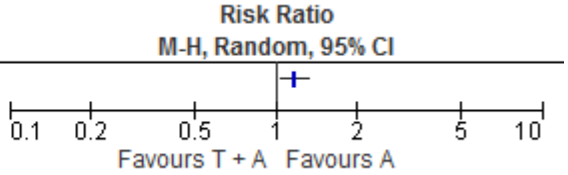


Figure 74: Treatment-related morbidity: neutropenic fever at 5.3 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GOIM 9902	24	363	10	354	2.34 [1.14, 4.82]

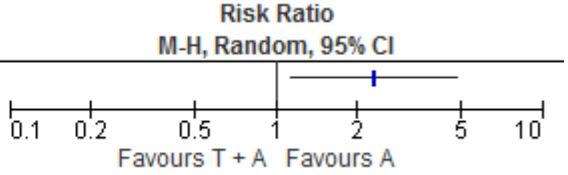


Figure 75: Treatment-related morbidity: hypersensitivity at 5.3 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GOIM 9902	19	363	1	354	18.53 [2.49, 137.67]

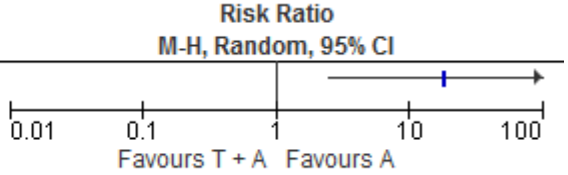
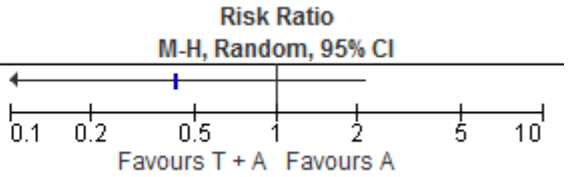


Figure 76: Treatment-related mortality at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
NSABP B-28	2	243	5	255	0.42 [0.08, 2.14]



Comparison 5. Epirubicin + paclitaxel versus FEC

Figure 77: Disease-free survival at 10 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
5.1.1 Mixed population							
GONO-MIG5	273	535	255	520	6.49	131.76	1.05 [0.89, 1.25]

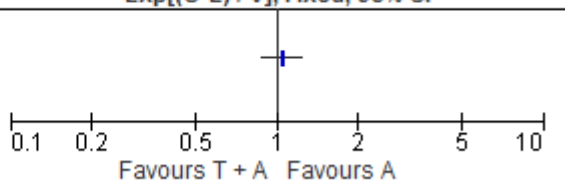
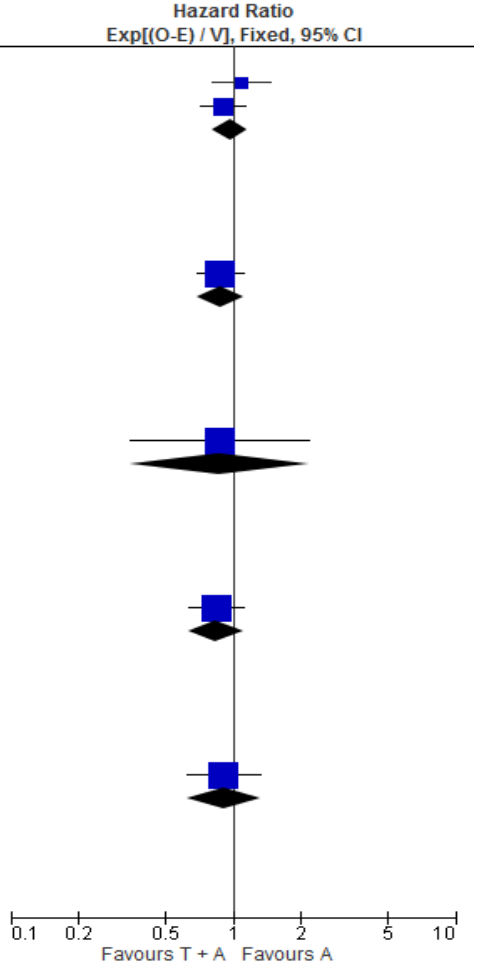


Figure 78: Overall survival at 10 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
5.2.1 Mixed population								
EBCTCG	91	1495	86	1515	3.64	42.29	37.7%	1.09 [0.81, 1.47]
GONO-MIG5	139	535	140	520	-6.96	69.87	62.3%	0.91 [0.72, 1.14]
Subtotal (95% CI)		**2030**		**2035**			**100.0%**	**0.97 [0.81, 1.17]**
Total events	230		226					
Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² = 0%								
Test for overall effect: Z = 0.31 (P = 0.75)								
5.2.2 T1/2; node positive								
GONO-MIG5	0	501	0	490	-8.37	65.49	100.0%	0.88 [0.69, 1.12]
Subtotal (95% CI)		**501**		**490**			**100.0%**	**0.88 [0.69, 1.12]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.03 (P = 0.30)								
5.2.3 T3/4; node positive								
GONO-MIG5	0	31	0	29	-0.62	4.43	100.0%	0.87 [0.34, 2.21]
Subtotal (95% CI)		**31**		**29**			**100.0%**	**0.87 [0.34, 2.21]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.29 (P = 0.77)								
5.2.4 Age <60; node positive								
GONO-MIG5	0	386	0	349	-8.35	47.9	100.0%	0.84 [0.63, 1.12]
Subtotal (95% CI)		**386**		**349**			**100.0%**	**0.84 [0.63, 1.12]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.21 (P = 0.23)								
5.2.5 Age 60+; node positive								
GONO-MIG5	0	149	0	171	-2.54	26.91	100.0%	0.91 [0.62, 1.33]
Subtotal (95% CI)		**149**		**171**			**100.0%**	**0.91 [0.62, 1.33]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.62)								



Note. Number of events in each arm not reported for subgroups based on tumour size or age

Figure 79: Treatment-related morbidity: anaemia at 10 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
GONO-MIG5	1	516	0	500	2.91 [0.12, 71.20]	

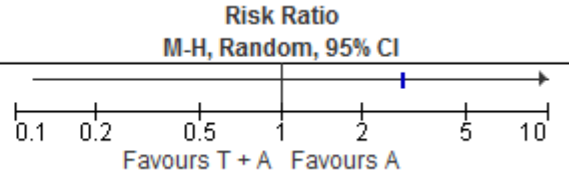


Figure 80: Treatment-related morbidity: leukopenia at 10 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
GONO-MIG5	91	516	86	500	1.03 [0.78, 1.34]	

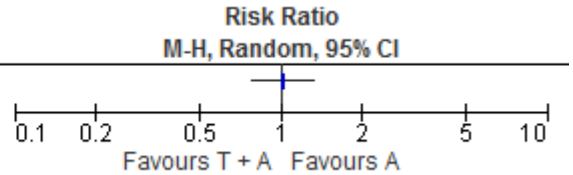


Figure 81: Treatment-related morbidity: neutropenia at 10 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
GONO-MIG5	11	516	15	500	0.71 [0.33, 1.53]	

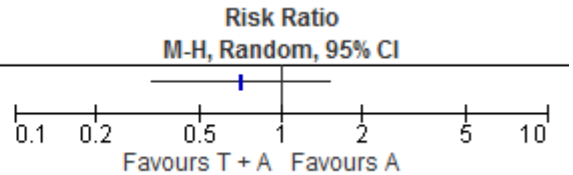


Figure 82: Treatment-related morbidity: febrile neutropenia at 10 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
GONO-MIG5	0	516	0	500	Not estimable	

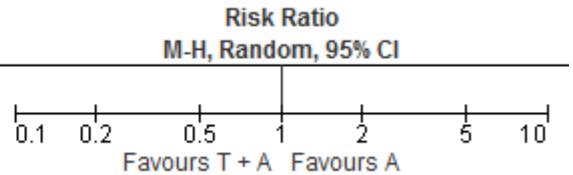


Figure 83: Treatment-related morbidity: thrombocytopenia at 10 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GONO-MIG5	4	516	13	500	0.30 [0.10, 0.91]

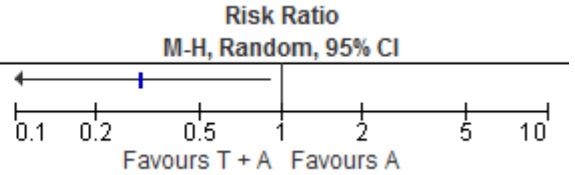


Figure 84: Treatment-related morbidity: lymphoma at 10 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GONO-MIG5	0	516	1	500	0.32 [0.01, 7.91]

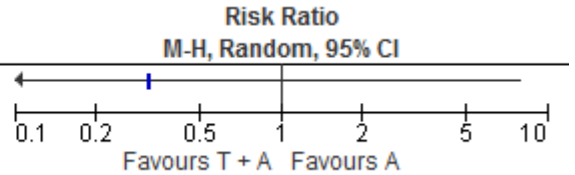


Figure 85: Treatment-related morbidity: acute leukaemia at 10 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GONO-MIG5	1	516	0	500	2.91 [0.12, 71.20]

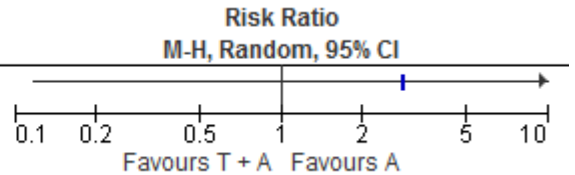


Figure 86: Treatment-related morbidity: nausea/vomiting at 10 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
GONO-MIG5	21	516	39	500	0.52 [0.31, 0.87]

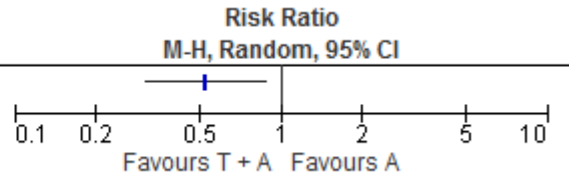


Figure 87: Treatment-related morbidity: diarrhoea at 10 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI
GONO-MIG5	1	516	2	500	0.48 [0.04, 5.33]

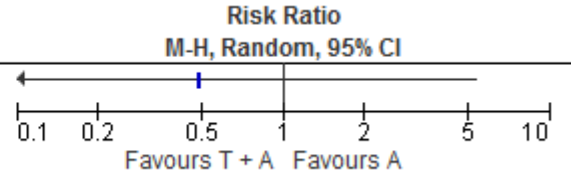


Figure 88: Treatment-related morbidity: hypersensitivity at 10 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI
GONO-MIG5	3	516	1	500	2.91 [0.30, 27.85]

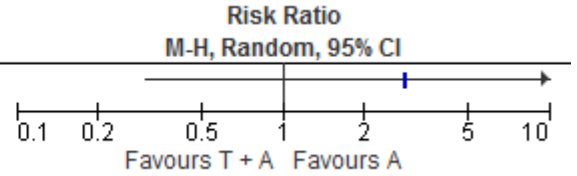


Figure 89: Treatment-related morbidity: neurological at 10 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI
GONO-MIG5	4	516	0	500	8.72 [0.47, 161.57]

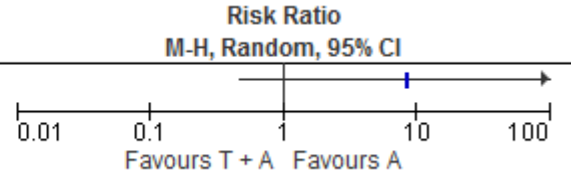
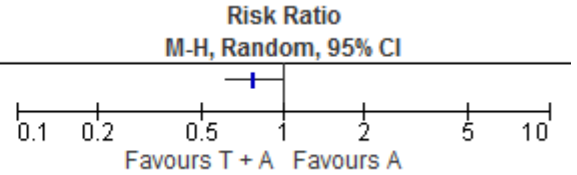


Figure 90: Adequate dose intensity: dose reductions and/or treatment delays

	Taxane + anthracycline		Anthracycline only		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI
GONO-MIG5	94	535	117	520	0.78 [0.61, 1.00]



Comparison 6. Doxorubicin + docetaxel versus AC

Figure 91: Overall survival (follow-up NR)

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
EBCTCG	184	1787	194	1792	-5.91	95.5	0.94 [0.77, 1.15]

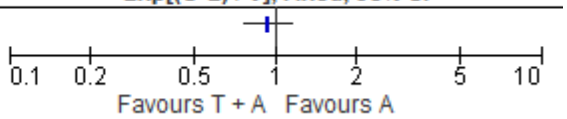


Figure 92: Treatment-related morbidity: febrile neutropenia at 2 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
RAPP 01	126	311	22	316	5.82 [3.80, 8.90]

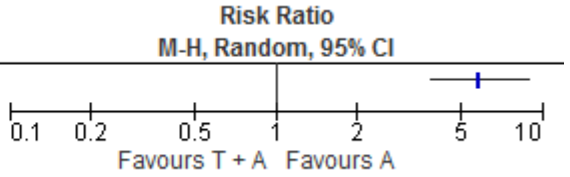


Figure 93: Treatment-related morbidity: nausea/vomiting at 2 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
RAPP 01	17	311	30	316	0.58 [0.32, 1.02]

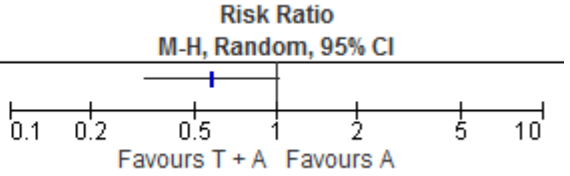
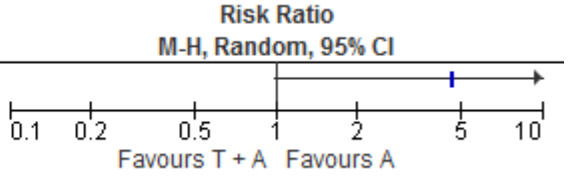


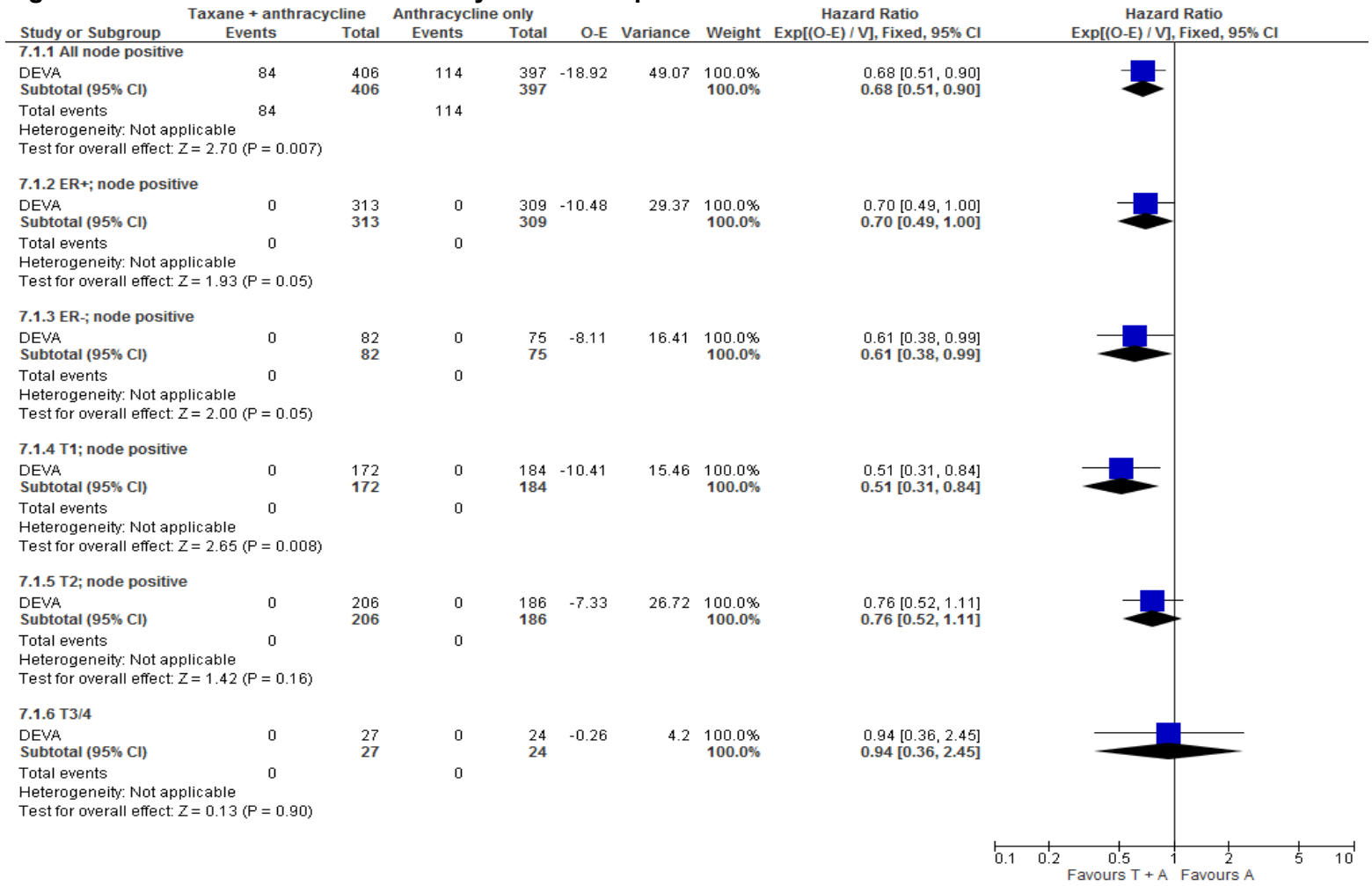
Figure 94: Treatment-related morbidity: diarrhoea at 2 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
RAPP 01	9	311	2	316	4.57 [1.00, 20.99]



Comparison 7. Epirubicin + docetaxel versus epirubicin

Figure 95: Disease-free survival at 5.4 year follow-up



Note. Number of events in each arm not reported for subgroups based on oestrogen receptor (ER) status or tumour size

Figure 96: Overall survival at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
7.2.1 All node positive							
DEVA	52	406	75	397	-12.5	30.09	0.66 [0.46, 0.94]

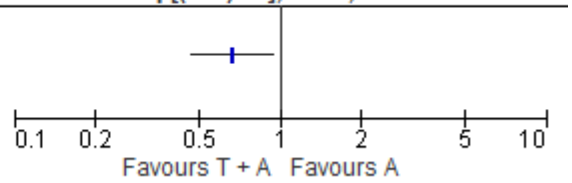


Figure 97: Treatment-related morbidity: anaemia at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
DEVA	126	396	125	377	0.96 [0.78, 1.18]

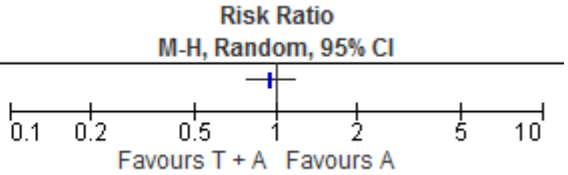


Figure 98: Treatment-related morbidity: acute myeloid leukaemia at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
DEVA	0	396	1	377	0.32 [0.01, 7.77]

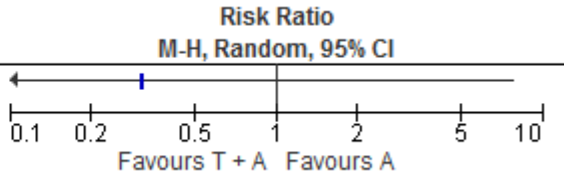


Figure 99: Treatment-related morbidity: febrile neutropenia at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
DEVA	51	396	7	377	6.94 [3.19, 15.09]

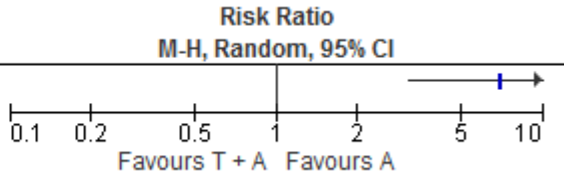


Figure 100: Treatment-related morbidity: leukopenia at 5.4 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
DEVA	99	396	83	377	1.14 [0.88, 1.47]	

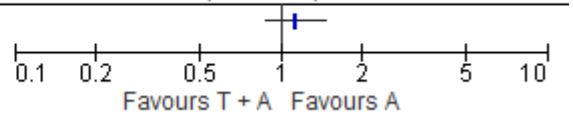


Figure 101: Treatment-related morbidity: neutropenia at 5.4 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
DEVA	54	396	54	377	0.95 [0.67, 1.35]	

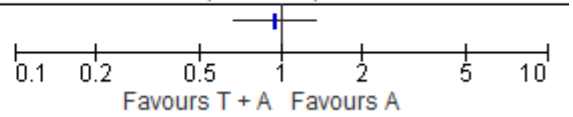


Figure 102: Treatment-related morbidity: thrombocytopenia at 5.4 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
DEVA	1	396	3	377	0.32 [0.03, 3.04]	

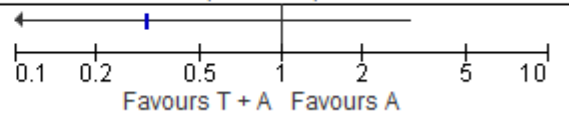


Figure 103: Treatment-related morbidity: diarrhoea at 5.4 year follow-up

	Taxane + anthracycline		Anthracycline only		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
DEVA	70	396	21	377	3.17 [1.99, 5.06]	

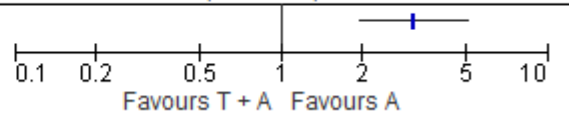


Figure 104: Treatment-related morbidity: lethargy at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
DEVA	25	396	15	377	1.59 [0.85, 2.96]

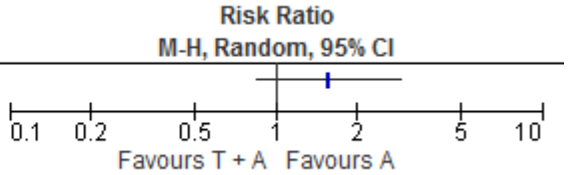


Figure 105: Treatment-related morbidity: nausea/vomiting at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
DEVA	179	396	211	377	0.81 [0.70, 0.93]

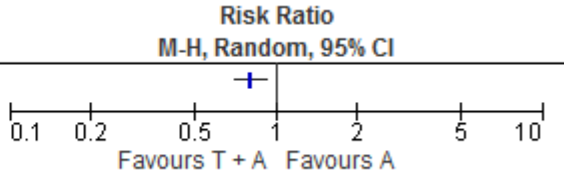


Figure 106: Treatment-related morbidity: peripheral neuropathy at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
DEVA	52	396	8	377	6.19 [2.98, 12.85]

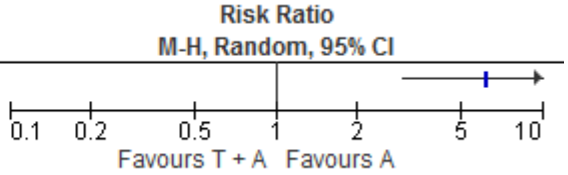


Figure 107: Treatment-related morbidity: unspecified neurological at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
DEVA	67	396	35	377	1.82 [1.24, 2.67]

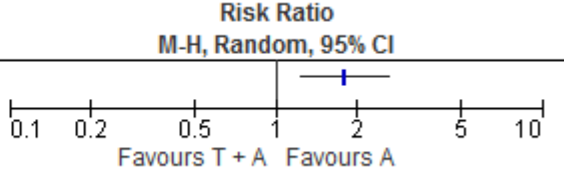


Figure 108: Adequate dose intensity: received 85% of planned dose

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
7.14.1 Cycles 1-3					
DEVA	384	406	365	397	1.03 [0.99, 1.07]
7.14.2 Cycles 4-6					
DEVA	309	406	334	397	0.90 [0.84, 0.97]

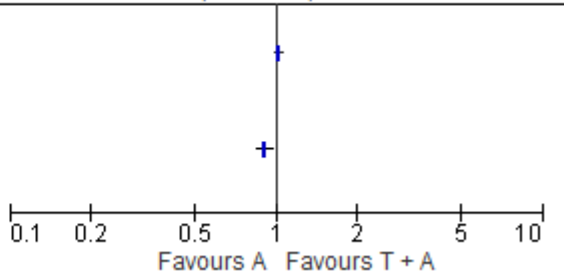


Figure 109: HRQoL: change in global health status from baseline (as measured by EORTC QoL) at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Mean	SD	Total	Anthracycline only Mean	SD	Total	Mean Difference IV, Random, 95% CI
DEVA	-0.26	23.57	63	-0.51	23.16	49	0.25 [-8.46, 8.96]

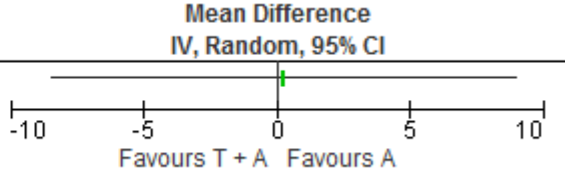


Figure 110: HRQoL: change in physical functioning from baseline (as measured by EORTC QoL) at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Mean	SD	Total	Anthracycline only Mean	SD	Total	Mean Difference IV, Random, 95% CI
DEVA	2.31	10.12	65	6.53	11.89	49	-4.22 [-8.36, -0.08]

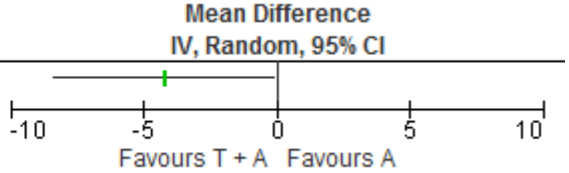


Figure 111: HRQoL: change in role functioning from baseline (as measured by EORTC QoL) at 5.4 year follow-up

Study or Subgroup	Taxane + anthracycline Mean	SD	Total	Anthracycline only Mean	SD	Total	Mean Difference IV, Random, 95% CI
DEVA	-3.85	29.43	65	-12.24	35.32	49	8.39 [-3.82, 20.60]

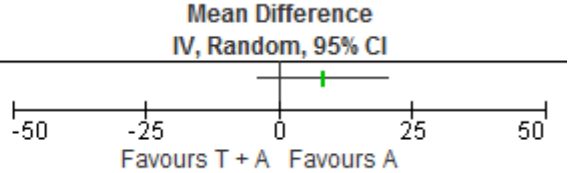


Figure 112: HRQoL: change in emotional functioning from baseline (as measured by EORTC QoL) at 5.4 year follow-up

	Taxane + anthracycline			Anthracycline only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
DEVA	-5.6	26.65	64	-10.49	21.75	49	4.89 [-4.04, 13.82]	

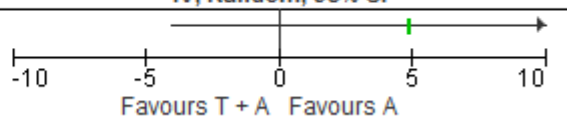


Figure 113: HRQoL: change in cognitive functioning from baseline (as measured by EORTC QoL) at 5.4 year follow-up

	Taxane + anthracycline			Anthracycline only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
DEVA	4.17	24.85	64	5.1	28.3	49	-0.93 [-10.92, 9.06]	

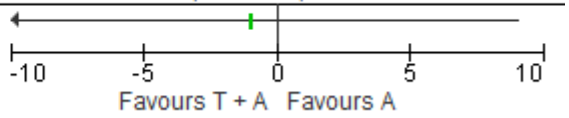


Figure 114: HRQoL: change in social functioning from baseline (as measured by EORTC QoL) at 5.4 year follow-up

	Taxane + anthracycline			Anthracycline only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
DEVA	-1.04	24.82	64	-6.6	29.72	48	5.56 [-4.82, 15.94]	

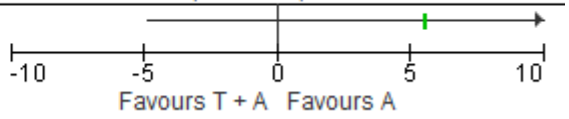


Figure 115: HRQoL: change in fatigue from baseline (as measured by EORTC QoL) at 5.4 year follow-up

	Taxane + anthracycline			Anthracycline only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
DEVA	-3.16	22.88	65	0	24.22	49	-3.16 [-11.93, 5.61]	

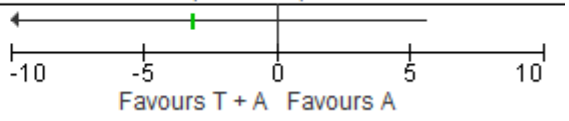


Figure 116: HRQoL: change in nausea and vomiting from baseline (as measured by EORTC QoL) at 5.4 year follow-up

	Taxane + anthracycline			Anthracycline only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
DEVA	0.26	14.58	65	1.02	18.76	49	-0.76 [-7.10, 5.58]	

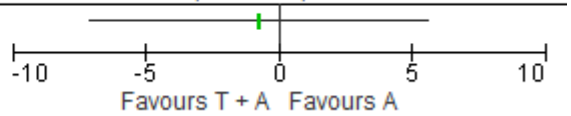


Figure 117: HRQoL: change in diarrhoea from baseline (as measured by EORTC QoL) at 5.4 year follow-up

	Taxane + anthracycline			Anthracycline only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
DEVA	-6.35	24.58	63	-9.52	22.57	49	3.17 [-5.59, 11.93]	

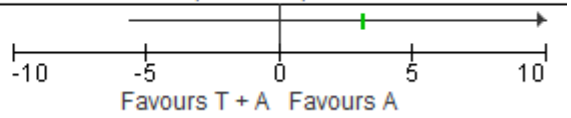
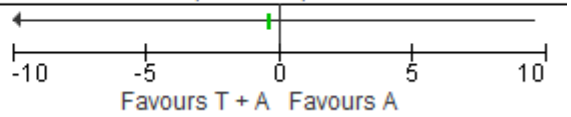


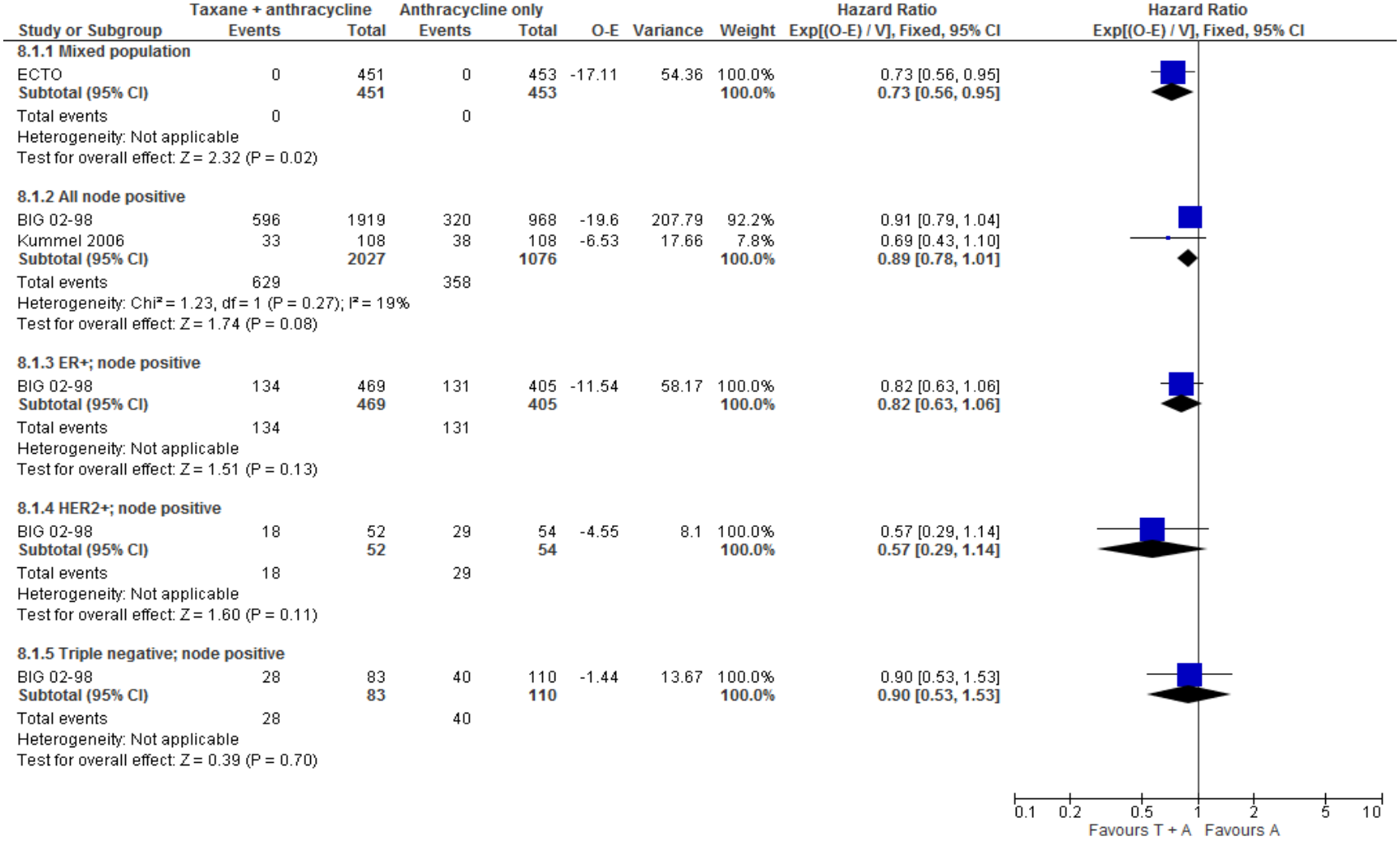
Figure 118: HRQoL: change in body image from baseline (as measured by EORTC QoL) at 5.4 year follow-up

	Taxane + anthracycline			Anthracycline only			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
DEVA	2.78	29.45	58	3.15	22.07	45	-0.37 [-10.32, 9.58]	



Comparison 8. Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF versus doxorubicin/epirubicin (± cyclophosphamide) + CMF

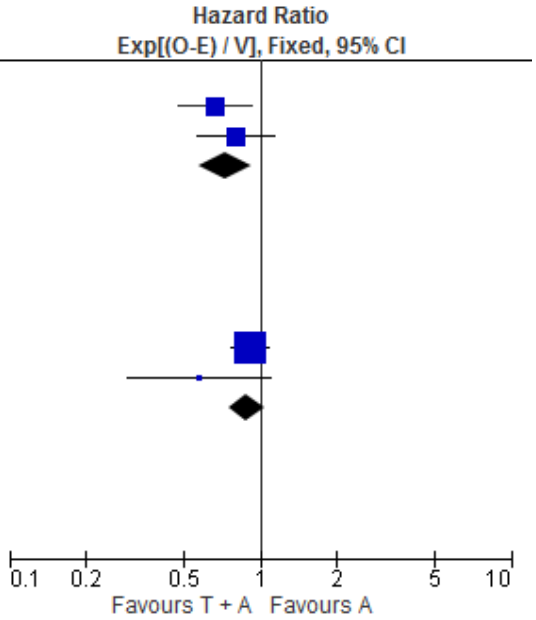
Figure 119: Disease-free survival at 3.2 to 8 year follow-up



Note. Number of events not reported in each arm in the ECTO trial

Figure 120: Overall survival at 3.2 to 8 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
8.2.1 Mixed population								
EBCTCG	57	486	85	486	-13.71	32.99	52.0%	0.66 [0.47, 0.93]
ECTO	0	451	0	453	-6.79	30.41	48.0%	0.80 [0.56, 1.14]
Subtotal (95% CI)		**937**		**939**			**100.0%**	**0.72 [0.57, 0.93]**
Total events	57		85					
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² = 0%								
Test for overall effect: Z = 2.57 (P = 0.01)								
8.2.2 All node positive								
BIG 02-98	366	1919	200	968	-12.66	134.24	93.8%	0.91 [0.77, 1.08]
Kummel 2006	15	108	22	108	-5.03	8.92	6.2%	0.57 [0.30, 1.10]
Subtotal (95% CI)		**2027**		**1076**			**100.0%**	**0.88 [0.75, 1.04]**
Total events	381		222					
Heterogeneity: Chi² = 1.84, df = 1 (P = 0.17); I² = 46%								
Test for overall effect: Z = 1.48 (P = 0.14)								



Note. Number of events not reported in each arm in the ECTO trial

Figure 121: Treatment-related morbidity: febrile neutropenia at 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
BIG 02-98	269	1919	63	968	2.15 [1.66, 2.80]

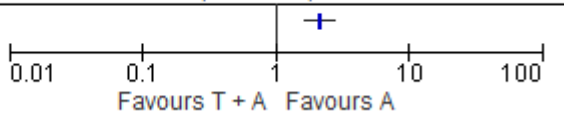


Figure 122: Treatment-related morbidity: neutropenia at 3.2 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
Kummel 2006	48	108	53	108	0.91 [0.68, 1.20]

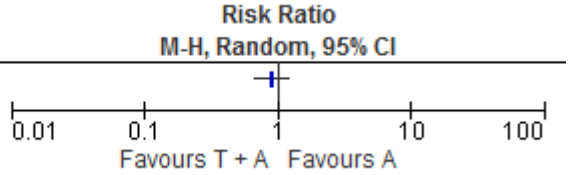


Figure 123: Treatment-related morbidity: anaemia at 3.2 to 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.5.1 Doxorubicin + docetaxel + CMF vs. doxorubicin (+/- cyclophosphamide) + CMF						
BIG 02-98	58	1919	48	968	66.7%	0.61 [0.42, 0.89]
Subtotal (95% CI)		**1919**		**968**	**66.7%**	**0.61 [0.42, 0.89]**
Total events	58		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.59 (P = 0.010)						
8.5.2 Epirubicin + paclitaxel + CMF vs. epirubicin + cyclophosphamide + CMF						
Kummel 2006	4	108	1	108	33.3%	4.00 [0.45, 35.21]
Subtotal (95% CI)		**108**		**108**	**33.3%**	**4.00 [0.45, 35.21]**
Total events	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
Total (95% CI)		**2027**		**1076**	**100.0%**	**1.14 [0.20, 6.52]**
Total events	62		49			
Heterogeneity: Tau² = 1.15; Chi² = 2.81, df = 1 (P = 0.09); I² = 64%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Chi² = 2.79, df = 1 (P = 0.09), I² = 64.2%						

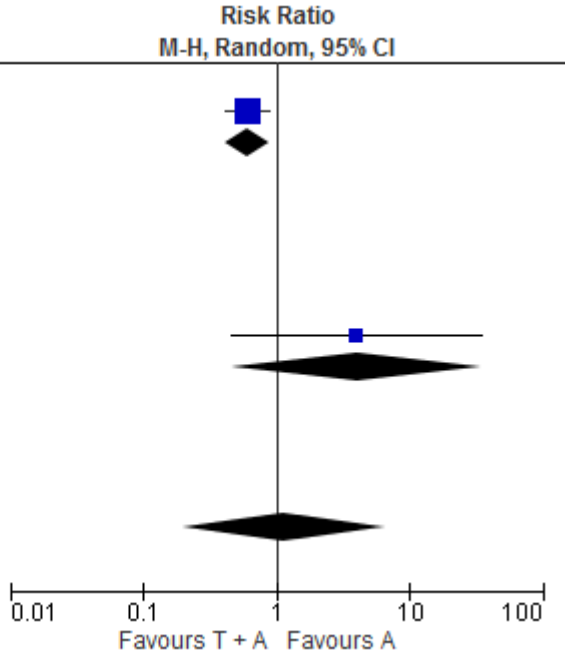


Figure 124: Treatment-related morbidity: thrombocytopenia at 3.2 to 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
BIG 02-98	77	1919	24	968	97.7%	1.62 [1.03, 2.54]
Kummel 2006	3	108	0	108	2.3%	7.00 [0.37, 133.91]
Total (95% CI)		**2027**		**1076**	**100.0%**	**1.67 [1.07, 2.62]**
Total events	80		24			

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 2.26 (P = 0.02)

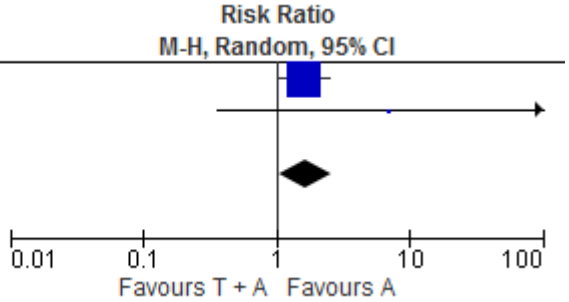


Figure 125: Treatment-related morbidity: leukopenia at 3.2 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
Kummel 2006	48	108	52	108	0.92 [0.69, 1.23]

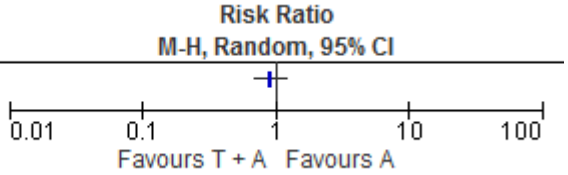


Figure 126: Treatment-related morbidity: hypersensitivity at 5 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
BIG 02-98	25	1919	0	968	25.74 [1.57, 422.33]

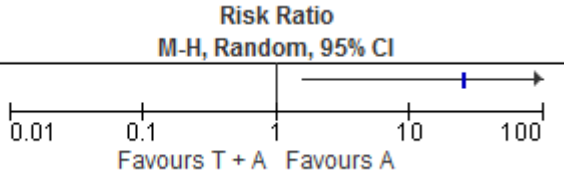


Figure 127: Treatment-related morbidity: nausea/vomiting at 3.2 year follow-up

Study or Subgroup	Taxane + anthracycline Events	Total	Anthracycline only Events	Total	Risk Ratio M-H, Random, 95% CI
Kummel 2006	7	108	12	108	0.58 [0.24, 1.43]

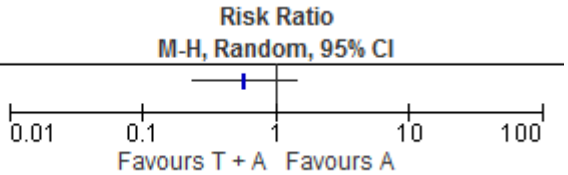


Figure 128: Treatment-related morbidity: diarrhoea at 5 year follow-up

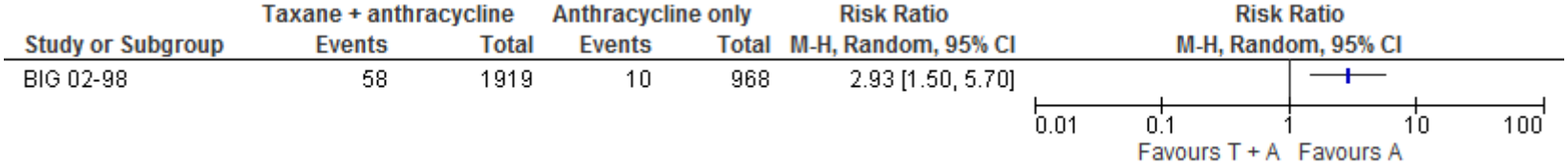


Figure 129: Treatment-related morbidity: neurosensory at 3.2 to 5 year follow-up

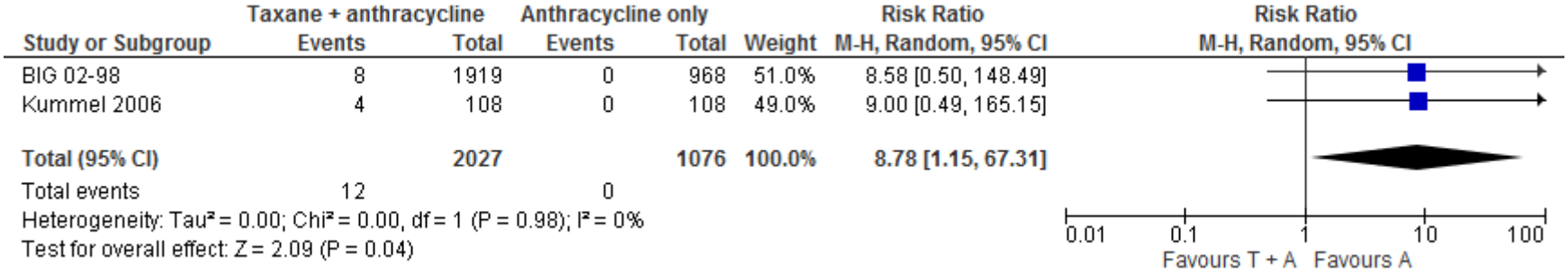


Figure 130: Treatment-related morbidity: fatigue at 3.2 year follow-up

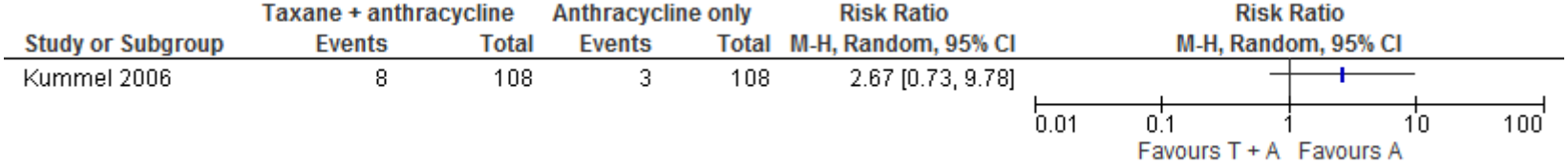


Figure 131: Treatment-related mortality at 5 year follow-up

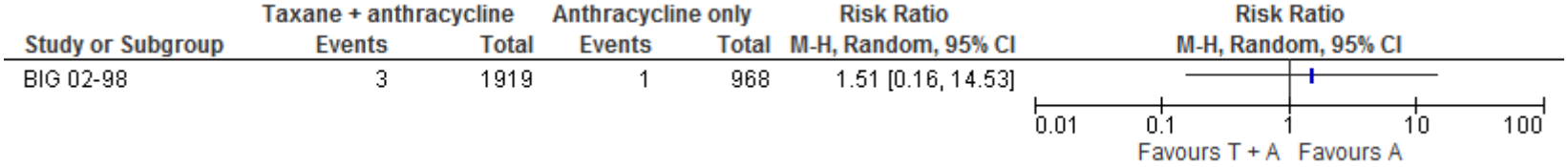
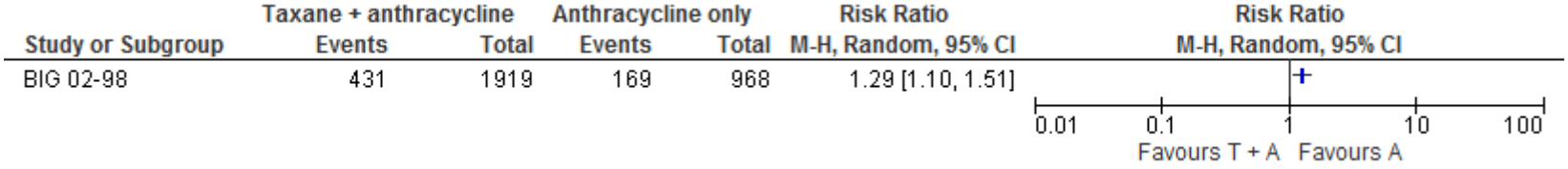


Figure 132: Adequate dose intensity: dose reductions



Appendix F – GRADE tables

2 **Table 15: Clinical evidence profile: Comparison 1. EC + docetaxel versus FEC**

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EC + docetaxel	FEC	Relative (95% CI)	Absolute	Quality	Importance
DFS – All node positive (5 year follow-up)												
3	Randomised trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	424/2034 (20.8%)	414/1842 (22.5%)	HR 0.92 (0.81 to 1.06)	16 fewer per 1000 (from 38 fewer to 12 more)	MODERATE	CRITICAL
DFS - ER+; node positive (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	-	-	HR 0.52 (0.26 to 1.04)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - ER-; node positive (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	-	-	HR 0.49 (0.22 to 1.08)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - HER2+; node positive (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	59/149 (39.6%)	53/153 (34.6%)	HR 1.16 (0.8 to 1.69)	43 more per 1000 (from 58 fewer to 166 more)	MODERATE	CRITICAL
DFS - HER2-; node positive (5 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EC + docetaxel	FEC	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	138/476 (29%)	126/473 (26.6%)	HR 1.06 (0.83 to 1.35)	14 more per 1000 (from 40 fewer to 75 more)	MODERATE	CRITICAL
DFS - Triple negative; node positive (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	43/94 (45.7%)	40/86 (46.5%)	HR 0.87 (0.57 to 1.34)	45 fewer per 1000 (from 165 fewer to 103 more)	MODERATE	CRITICAL
OS - All node positive (5 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	114/1345 (8.5%)	127/1167 (10.9%)	HR 0.81 (0.62 to 1.04)	20 fewer per 1000 (from 40 fewer to 4 more)	MODERATE	CRITICAL
Treatment-related morbidity – neutropenia (5 year follow-up)												
2	Randomised trials	No serious risk of bias	Very serious[4]	No serious indirectness	Very serious[5]	None	679/1062 (63.9%)	580/1052 (55.1%)	RR 1.27 (0.72 to 2.26)	149 more per 1000 (from 154 fewer to 695 more)	VERY LOW	CRITICAL
Treatment-related morbidity - febrile neutropenia (5 year follow-up)												
2	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[3]	None	65/1356 (4.8%)	28/1173 (2.4%)	RR 2.05 (1.33 to 3.17)	25 more per 1000 (from 8 more to 52 more)	LOW	CRITICAL
Treatment-related morbidity – anaemia (5 year follow-up)												
2	Randomised trials	No serious	Very serious[7]	No serious indirectness	Very serious[8]	None	24/1062 (2.3%)	108/1052 (10.3%)	RR 0.49 (0.06 to 4.35)	52 fewer per 1000 (from 97	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EC + docetaxel	FEC	Relative (95% CI)	Absolute		
		risk of bias								fewer to 344 more)		
Treatment-related morbidity – thrombocytopenia (5 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	13/1062 (1.2%)	162/1052 (15.4%)	RR 0.08 (0.05 to 0.14)	142 fewer per 1000 (from 132 fewer to 146 fewer)	MODERATE	CRITICAL
Treatment-related morbidity – leukopenia (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	491/684 (71.8%)	542/674 (80.4%)	RR 0.89 (0.84 to 0.95)	88 fewer per 1000 (from 40 fewer to 129 fewer)	HIGH	CRITICAL
Treatment-related morbidity – nausea (5 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	31/1062 (2.9%)	29/1052 (2.8%)	RR 1.06 (0.62 to 1.8)	2 more per 1000 (from 10 fewer to 22 more)	LOW	CRITICAL
Treatment-related morbidity – vomiting (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[9]	None	24/684 (3.5%)	12/674 (1.8%)	RR 1.97 (0.99 to 3.91)	17 more per 1000 (from 0 fewer to 52 more)	LOW	CRITICAL
Treatment-related morbidity – diarrhoea (5 year follow-up)												
2	Randomised trials	No serious risk of bias	Very serious[10]	No serious indirectness	Very serious[8]	None	21/1062 (2%)	12/1052 (1.1%)	RR 3.44 (0.04 to 301.37)	28 more per 1000 (from 11 fewer to 1000 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EC + docetaxel	FEC	Relative (95% CI)	Absolute		
Treatment-related morbidity – hypersensitivity (5 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	5/1062 (0.47%)	0/1052 (0%)	RR 5.43 (0.63 to 46.87)	-	LOW	CRITICAL
Treatment-related morbidity – neurological (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	5/684 (0.73%)	1/674 (0.15%)	RR 4.93 (0.58 to 42.06)	6 more per 1000 (from 1 fewer to 61 more)	LOW	CRITICAL
Treatment-related mortality (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	0/378 (0%)	2/378 (0.53%)	RR 0.2 (0.01 to 4.15)	4 fewer per 1000 (from 5 fewer to 17 more)	LOW	IMPORTANT
Adequate dose intensity - dose reductions - All cycles												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[9]	None	66/378 (17.5%)	48/378 (12.7%)	RR 1.38 (0.98 to 1.94)	48 more per 1000 (from 3 fewer to 119 more)	LOW	IMPORTANT
Adequate dose intensity - dose reductions - 1st half of cycles												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	3/689 (0.4%)	22/675 (3.3%)	RR 0.13 (0.04 to 0.44)	28 fewer per 1000 (from 18 fewer to 31 fewer)	MODERATE	IMPORTANT
Adequate dose intensity - dose reductions - 2nd half of cycles												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	35/689 (5.1%)	64/675 (9.5%)	RR 0.54 (0.36 to 0.8)	44 fewer per 1000 (from 19 fewer to 61 fewer)	MODERATE	IMPORTANT
HRQoL - global health (measured by EORTC QLQ-30) (Better indicated by lower values) (5 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EC + docetaxel	FEC	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[12]	No serious inconsistency	No serious indirectness	No serious imprecision	None	305	263	-	MD 3.5 lower (7.02 lower to 0.02 higher)	MODERATE	IMPORTANT
HRQoL - physical functioning (measured by EORTC QLQ-30) (Better indicated by lower values) (5 year follow-up)												
1	Randomised trials	Serious[12]	No serious inconsistency	No serious indirectness	No serious imprecision	None	311	265	-	MD 4.3 lower (7.68 to 0.92 lower)	MODERATE	IMPORTANT
HRQoL - nausea and vomiting (measured by EORTC QLQ-30) (Better indicated by lower values) (5 year follow-up)												
1	Randomised trials	Serious[12]	No serious inconsistency	No serious indirectness	No serious imprecision	None	310	265	-	MD 4.3 lower (7.63 to 0.97 lower)	MODERATE	IMPORTANT
HRQoL - fatigue (measured by EORTC QLQ-30) (Better indicated by lower values) (5 year follow-up)												
1	Randomised trials	Serious[12]	No serious inconsistency	No serious indirectness	No serious imprecision	None	311	265	-	MD 4.8 higher (0.58 to 9.02 higher)	MODERATE	IMPORTANT
HRQoL - systemic therapy side effects (measured by EORTC QLQ-30) (Better indicated by lower values) (5 year follow-up)												
1	Randomised trials	Serious[12]	No serious inconsistency	No serious indirectness	No serious imprecision	None	307	259	-	MD 5.5 higher (2.12 to 8.88 higher)	MODERATE	IMPORTANT

CI, confidence interval; DFS, disease-free survival; EC, epirubicin, cyclophosphamide; EORTC QLQ-30, European Organisation for Research and Treatment of Cancer quality of life questionnaire; ER, oestrogen receptor; FEC, flouroruacil, epirubicin, cyclophosphamide; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HRQoL, health-related quality of life; OS, overall survival; RR, risk ratio

[1] Significant heterogeneity - I2 78%; explored in subsequent subgroup analysis

[2] Cannot determine imprecision as number of events/people in subgroup not reported

[3] <300 events

[4] Significant heterogeneity - I2 98%; cannot explore as data for subgroups of interest not reported

[5] 95% confidence interval crosses boundary of no effect (1) and both minimally important differences (0.8 and 1.25) based on GRADE default values

[6] *High attrition in EC-Doc trial*
[7] *Significant heterogeneity - I2 88%; cannot explore as data for subgroups of interest not reported*
[8] *<300 events; 95% confidence interval crosses boundary for no effect (1) and both minimally important differences (0.8 and 1.25) based on GRADE default values*
[9] *<300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important difference (1.25) based on GRADE default values*
[10] *Significant heterogeneity - I2 89%; cannot explore as data for subgroups of interest not reported*
[11] *Significant heterogeneity - I2 90%; explored in subsequent subgroup analysis*
[12] *Risk of detection bias due to subjective, patient-reported outcome*

Table 16: Clinical evidence profile: Comparison 2. TAC versus FAC

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC	FAC	Relative (95% CI)	Absolute	Quality	Importance
DFS - All node negative (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	66/539 (12.2%)	95/521 (18.2%)	HR 0.74 (0.55 to 0.98)	44 fewer per 1000 (from 3 fewer to 78 fewer)	MODERATE	CRITICAL
DFS - T1; node negative (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/285 (0%)	0/250 (0%)	HR 0.69 (0.43 to 1.1)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - T2+; node negative (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/254 (0%)	0/271 (0%)	HR 0.68 (0.45 to 1.03)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - HER2+; node negative (6.4 year follow-up)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC	FAC	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/39 (0%)	0/44 (0%)	HR 0.73 (0.2 to 2.62)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - HER2-; node negative (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/190 (0%)	0/165 (0%)	HR 0.48 (0.25 to 0.91)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - Triple negative; node negative (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/90 (0%)	0/80 (0%)	HR 0.59 (0.32 to 1.08)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - All node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	283/745 (38%)	336/746 (45%)	HR 0.8 (0.68 to 0.94)	70 fewer per 1000 (from 20 fewer to 116 fewer)	HIGH	CRITICAL
DFS - HER2+; node positive (10 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC	FAC	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/155 (0%)	0/164 (0%)	HR 0.6 (0.43 to 0.83)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - HER2-; node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/513 (0%)	0/492 (0%)	HR 0.9 (0.74 to 1.1)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - Triple negative; node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/99 (0%)	0/93 (0%)	HR 0.84 (0.56 to 1.25)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - All node negative (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	26/539 (4.8%)	34/521 (6.5%)	HR 0.76 (0.45 to 1.27)	15 fewer per 1000 (from 35 fewer to 17 more)	MODERATE	CRITICAL
OS - All node positive (10 year follow-up)												
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	179/745 (24%)	231/746 (31%)	HR 0.74 (0.61 to 0.9)	70 fewer per 1000 (from 26	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC	FAC	Relative (95% CI)	Absolute		
		risk of bias								fewer to 107 fewer)		
OS - HER2+; node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/155 (0%)	0/164 (0%)	HR 0.63 (0.43 to 0.93)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - HER2-; node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/513 (0%)	0/492 (0%)	HR 0.81 (0.64 to 1.02)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - Triple negative; node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/99 (0%)	0/93 (0%)	HR 0.81 (0.51 to 1.28)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Treatment-related morbidity – neutropenia (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	378/532 (71.1%)	417/519 (80.3%)	RR 0.88 (0.83 to 0.95)	96 fewer per 1000 (from 40 fewer to	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC	FAC	Relative (95% CI)	Absolute		
										137 fewer)		
Treatment-related morbidity - febrile neutropenia (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	51/532 (9.6%)	12/519 (2.3%)	RR 4.15 (2.24 to 7.69)	73 more per 1000 (from 29 more to 155 more)	MODERATE	CRITICAL
Treatment-related morbidity - neutropenic fever (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	35/532 (6.6%)	14/519 (2.7%)	RR 2.44 (1.33 to 4.48)	39 more per 1000 (from 9 more to 94 more)	MODERATE	CRITICAL
Treatment-related morbidity – anaemia (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	504/532 (94.7%)	360/519 (69.4%)	RR 1.37 (1.29 to 1.45)	257 more per 1000 (from 201 more to 312 more)	HIGH	CRITICAL
Treatment-related morbidity – leukopenia (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	456/532 (85.7%)	439/519 (84.6%)	RR 1.01 (0.96 to 1.07)	8 more per 1000 (from 34 fewer to 59 more)	HIGH	CRITICAL
Treatment-related morbidity – thrombocytopenia (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	64/532 (12%)	26/519 (5%)	RR 2.4 (1.55 to 3.73)	70 more per 1000 (from 28 more to 137 more)	MODERATE	CRITICAL
Treatment-related morbidity – nausea (6.4 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC	FAC	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	379/532 (71.2%)	387/519 (74.6%)	RR 0.96 (0.89 to 1.03)	30 fewer per 1000 (from 82 fewer to 22 more)	HIGH	CRITICAL
Treatment-related morbidity – vomiting (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	292/532 (54.9%)	294/519 (56.6%)	RR 0.97 (0.87 to 1.08)	17 fewer per 1000 (from 74 fewer to 45 more)	HIGH	CRITICAL
Treatment-related morbidity – diarrhoea (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	147/532 (27.6%)	70/519 (13.5%)	RR 2.05 (1.58 to 2.65)	142 more per 1000 (from 78 more to 223 more)	MODERATE	CRITICAL
Treatment-related morbidity - peripheral sensory neuropathy (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	83/632 (13.1%)	38/519 (7.3%)	RR 1.79 (1.24 to 2.59)	58 more per 1000 (from 18 more to 116 more)	MODERATE	CRITICAL
Treatment-related morbidity - peripheral motor neuropathy (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	18/532 (3.4%)	2/519 (0.39%)	RR 8.78 (2.05 to 37.65)	30 more per 1000 (from 4 more to 141 more)	MODERATE	CRITICAL
Treatment-related morbidity – hypersensitivity (6.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	23/532 (4.3%)	8/519 (1.5%)	RR 2.8 (1.27 to 6.21)	28 more per 1000 (from 4	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC	FAC	Relative (95% CI)	Absolute		
										more to 80 more)		
Treatment-related morbidity - acute myeloid leukaemia (10.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	4/744 (0.54%)	1/736 (0.14%)	RR 3.96 (0.44 to 35.32)	4 more per 1000 (from 1 fewer to 47 more)	LOW	CRITICAL
Treatment-related morbidity - chronic lymphocytic leukaemia (10.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	0/744 (0%)	1/736 (0.14%)	RR 0.33 (0.01 to 8.08)	1 fewer per 1000 (from 1 fewer to 10 more)	LOW	CRITICAL
Treatment-related morbidity – myelodysplasia (10.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	2/744 (0.27%)	1/736 (0.14%)	RR 1.98 (0.18 to 21.77)	1 more per 1000 (from 1 fewer to 28 more)	LOW	CRITICAL

CI, confidence interval; DFS, disease-free survival; FAC, fluorouracil, doxorubicin, cyclophosphamide; HR, hazard ratio; OS, overall survival; RR, risk ratio; TAC, docetaxel; doxorubicin, cyclophosphamide

[1] <300 events

[2] Cannot judge imprecision as number of events not reported

[3] <300 events; 95% confidence interval crosses boundary for no effect (1) and both minimally important differences (0.8 and 1.25) based on GRADE default values

Table 17: Clinical evidence profile: Comparison 3. FEC/FAC + docetaxel/paclitaxel versus FEC/FAC

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
DFS - Mixed population: direct evidence (5 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	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
3	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	249/1198 (20.8%)	309/1211 (25.5%)	HR 0.72 (0.61 to 0.86)	64 fewer per 1000 (from 31 fewer to 91 fewer)	MODERATE	CRITICAL
DFS - Mixed population: indirect evidence (comparison) (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	517/2073 (24.9%)	539/2089 (25.8%)	HR 0.95 (0.84 to 1.07)	11 fewer per 1000 (from 36 fewer to 15 more)	MODERATE	CRITICAL
DFS - ER+ (5 year follow-up)												
1	Randomised trials		No serious inconsistency	Serious[2]	[3]	None	-	-	HR 1.02 (0.87 to 1.19)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - ER- (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	[3]	None	-	-	HR 0.87 (0.72 to 1.05)	-	Number of events was not reported - insufficient information	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute	Quality	Importance
											to judge imprecision, and therefore overall quality	
DFS - HER2+ (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	[3]	None	-	-	HR 0.87 (0.69 to 1.09)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - HER2- (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	[3]	None	-	-	HR 1.02 (0.87 to 1.19)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - Node negative (5 year follow-up)												
2	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[5]	None	67/951 (7%)	94/974 (9.7%)	HR 0.79 (0.62	19 fewer per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
									to 0.99)	(from 1 fewer to 36 fewer)		
DFS - Node positive (5 to 10 year follow-up)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	446/1597 (27.9%)	488/1588 (30.7%)	HR 0.92 (0.84 to 1.01)	21 fewer per 1000 (from 42 fewer to 3 more)	HIGH	CRITICAL
DFS - Aged <60 (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	[3]	None	-	-	HR 1 (0.99 to 1.01)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - Aged 60+ (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	[3]	None	-	-	HR 0.9 (0.63 to 1.29)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute	Quality	Importance
											overall quality	
DFS - T1 (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	[3]	None	-	-	HR 0.87 (0.68 to 1.11)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - T2 (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	[3]	None	-	-	HR 0.97 (0.83 to 1.13)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - T3/4 (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	[3]	None	-	-	HR 0.91 (0.66 to 1.26)	-	Number of events was not reported - insufficient information to judge imprecision, and	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute	Quality	Importance
											therefore overall quality	
DFS - Triple negative; node positive (8 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	[3]	None	-	-	HR 0.88 (0.49 to 1.58)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - Mixed population (5 to 10 year follow-up)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	473/3271 (14.5%)	529/3300 (16%)	HR 0.9 (0.8 to 1.01)	15 fewer per 1000 (from 30 fewer to 1 more)	HIGH	CRITICAL
OS - Node negative (5 year follow-up)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[5]	None	31/951 (3.3%)	40/974 (4.1%)	HR 0.79 (0.49 to 1.27)	8 fewer per 1000 (from 21 fewer to 11 more)	LOW	CRITICAL
OS - All node positive (8 to 10 year follow-up)												
3	Randomised trials	No seriou	No serious inconsistency	No serious indirectness	No serious imprecision	None	283/1597 (17.7%)	345/1588 (21.7%)	HR 0.79	41 fewer	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
		s risk of bias							(0.68 to 0.93)	per 1000 (from 14 fewer to 64 fewer)		
OS - T stage 1; node positive (8 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	-	-	HR 0.74 (0.44 to 1.24)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - T stage 2+; node positive (8 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	-	-	HR 0.81 (0.64 to 1.03)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - ER+; node positive (8 year follow-up)												
1	Randomised trials	No serious risk	No serious inconsistency	No serious indirectness	[3]	None	-	-	HR 0.79 (0.62	-	Number of events was not reported - insufficient	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute	Quality	Importance
		of bias							to 1.01)		information to judge imprecision, and therefore overall quality	
OS - ER-; node positive (8 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	-	-	HR 0.72 (0.5 to 1.03)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - HER2+; node positive (8 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	-	-	HR 0.5 (0.27 to 0.91)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - HER2-; node positive (8 year follow-up)												
1	Randomised trials	No serious risk	No serious inconsistency	No serious indirectness	[3]	None	-	-	HR 1.32 (0.98	-	Number of events was not reported	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute	Quality	Importance
		of bias							to 1.76)		- insufficient information to judge imprecision, and therefore overall quality	
Treatment-related morbidity – neutropenia (5 to 9 year follow-up)												
6	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	1894/5326 (35.6%)	1961/5455 (35.9%)	RR 0.91 (0.79 to 1.06)	32 fewer per 1000 (from 75 fewer to 22 more)	MODERATE	CRITICAL
Treatment-related morbidity - neutropenia - Direct evidence (5 to 9 year follow-up)												
5	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	957/3253 (29.4%)	1164/3366 (34.6%)	RR 0.87 (0.78 to 0.96)	45 fewer per 1000 (from 14 fewer to 76 fewer)	HIGH	CRITICAL
Treatment-related morbidity - neutropenia - Indirect evidence (comparison) (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	937/2073 (45.2%)	797/2089 (38.2%)	RR 1.18 (1.1 to 1.27)	69 more per 1000 (from 38 more to 103 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
Treatment-related morbidity - febrile neutropenia (5 to 9 year follow-up)												
5	Randomised trials	No serious risk of bias	Very serious[7]	No serious indirectness	Very serious[8]	None	346/4395 (7.9%)	260/4469 (5.8%)	RR 1.18 (0.71 to 1.94)	10 more per 1000 (from 17 fewer to 55 more)	VERY LOW	CRITICAL
Treatment-related morbidity - febrile neutropenia - Direct evidence (5 to 9 year follow-up)												
4	Randomised trials	No serious risk of bias	Serious[9]	No serious indirectness	Very serious[8]	None	200/2322 (8.6%)	199/2380 (8.4%)	RR 0.97 (0.63 to 1.5)	3 fewer per 1000 (from 31 fewer to 42 more)	VERY LOW	CRITICAL
Treatment-related morbidity - febrile neutropenia - Indirect evidence (comparison) (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[5]	None	146/2073 (7%)	61/2089 (2.9%)	RR 2.41 (1.8 to 3.23)	41 more per 1000 (from 23 more to 65 more)	LOW	CRITICAL
Treatment-related morbidity – anaemia (5 to 8 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[10]	Very serious[11]	None	22/3404 (0.6%)	32/3411 (0.9%)	RR 0.69 (0.4 to 1.2)	3 fewer per 1000 (from 6 fewer to 2 more)	VERY LOW	CRITICAL
Treatment-related morbidity – thrombocytopenia (5 to 9 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[12]	None	94/3781 (2.5%)	120/3837 (3.1%)	RR 0.8 (0.49 to 1.3)	6 fewer per 1000 (from 16 fewer to 9 more)	LOW	CRITICAL
Treatment-related morbidity – leukopenia (5 to 9 year follow-up)												
2	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[11]	None	104/1308 (8%)	122/1412 (8.6%)	RR 0.92 (0.71 to 1.18)	7 fewer per 1000 (from 25 fewer to 16 more)	VERY LOW	CRITICAL
Treatment-related morbidity – lymphopenia (5 year follow-up)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[12]	None	9/931 (0.97%)	10/986 (1%)	RR 0.95 (0.39 to 2.34)	1 fewer per 1000 (from 6 fewer to 14 more)	VERY LOW	CRITICAL
Treatment-related morbidity – vomiting (5 to 9 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[6]	None	248/1922 (12.9%)	309/2044 (15.1%)	RR 0.89 (0.78 to 1.01)	17 fewer per 1000 (from 33 fewer to 2 more)	MODERATE	CRITICAL
Treatment-related morbidity – nausea (5 to 9 year follow-up)												
3	Randomised trials	No serious risk	No serious inconsistency	No serious indirectness	No serious imprecision	None	351/1922 (18.3%)	411/2044 (20.1%)	RR 0.95 (0.89	10 fewer per	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
		of bias							to 1.02)	1000 (from 22 fewer to 4 more)		
Treatment-related morbidity - nausea/vomiting (5 to 8 year follow-up)												
3	Randomised trials	No serious risk of bias	Very serious[13]	No serious indirectness	Serious[6]	None	348/3404 (10.2%)	471/3411 (13.8%)	RR 0.69 (0.45 to 1.05)	43 fewer per 1000 (from 76 fewer to 7 more)	VERY LOW	CRITICAL
Treatment-related morbidity - nausea/vomiting - Direct evidence (5 to 8 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	149/1331 (11.2%)	266/1322 (20.1%)	RR 0.56 (0.46 to 0.67)	89 fewer per 1000 (from 66 fewer to 109 fewer)	HIGH	CRITICAL
Treatment-related morbidity - nausea/vomiting - Indirect evidence (comparison) (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	199/2073 (9.6%)	205/2089 (9.8%)	RR 0.98 (0.81 to 1.18)	2 fewer per 1000 (from 19 fewer to 18 more)	MODERATE	CRITICAL
Treatment-related morbidity – diarrhoea (5 to 9 year follow-up)												
2	Randomised trials	No serious risk	No serious inconsistency	Serious[10]	Very serious[12]	None	92/2450 (3.8%)	80/2515 (3.2%)	RR 1.12 (0.71	4 more per 1000 (from 9	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
		of bias							to 1.76)	fewer to 24 more)		
Treatment-related morbidity – lethargy (5 to 9 year follow-up)												
4	Randomised trials	No serious risk of bias	Very serious[14]	No serious indirectness	Very serious[8]	None	551/3995 (13.8%)	341/4133 (8.3%)	RR 1.3 (0.79 to 2.14)	25 more per 1000 (from 17 fewer to 94 more)	VERY LOW	CRITICAL
Treatment-related morbidity - lethargy - Direct evidence (5 year follow-up)												
3	Randomised trials	Serious[4]	Very serious[15]	No serious indirectness	Very serious[12]	None	95/1922 (4.9%)	69/2044 (3.4%)	RR 1.06 (0.39 to 2.87)	2 more per 1000 (from 21 fewer to 63 more)	VERY LOW	CRITICAL
Treatment-related morbidity - lethargy - Indirect evidence (comparison) (5 to 9 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	456/2073 (22%)	272/2089 (13%)	RR 1.69 (1.47 to 1.94)	90 more per 1000 (from 61 more to 122 more)	MODERATE	CRITICAL
Treatment-related morbidity – neuropathy (5 to 9 year follow-up)												
4	Randomised trials	No serious risk of bias	Serious[16]	No serious indirectness	No serious imprecision	None	517/3995 (12.9%)	29/4133 (0.7%)	RR 20.65 (7.02 to 60.74)	138 more per 1000 (from 42 more to	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
										419 more)		
Treatment-related morbidity - neuropathy - Direct evidence (5 to 9 year follow-up)												
3	Randomised trials	No serious risk of bias	Very serious[17]	No serious indirectness	No serious imprecision	None	419/1922 (21.8%)	18/2044 (0.9%)	RR 63.34 (3.83 to 1048.53)	549 more per 1000 (from 25 more to 1000 more)	LOW	CRITICAL
Treatment-related morbidity - neuropathy - Indirect evidence (comparison) (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[5]	None	98/2073 (4.7%)	11/2089 (0.5%)	RR 8.98 (4.83 to 16.69)	42 more per 1000 (from 20 more to 83 more)	LOW	CRITICAL
Treatment-related mortality (5 year follow-up)												
2	Randomised trials	Serious[4]	Very serious[18]	No serious indirectness	Very serious[12]	None	8/3004 (0.3%)	8/3075 (0.3%)	RR 1.24 (0.06 to 23.71)	1 more per 1000 (from 2 fewer to 59 more)	VERY LOW	IMPORTANT
Treatment-related mortality - Direct evidence (5 year follow-up)												
1	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[12]	None	2/931 (0.2%)	7/986 (0.7%)	RR 0.3 (0.06 to 1.45)	5 fewer per 1000 (from 7 fewer to 3 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FEC/FAC + docetaxel/paclitaxel	FEC/FAC	Relative (95% CI)	Absolute		
Treatment-related mortality - Indirect evidence (comparison) (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[12]	None	6/2073 (0.3%)	1/2089 (0%)	RR 6.05 (0.73 to 50.18)	2 more per 1000 (from 0 fewer to 24 more)	VERY LOW	IMPORTANT
Adequate dose intensity – dose reductions (all cycles)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	None	61/1003 (6.1%)	36/996 (3.6%)	RR 1.68 (1.13 to 2.52)	25 more per 1000 (from 5 more to 55 more)	MODERATE	IMPORTANT

CI, confidence interval; DFS, disease-free survival; ER, oestrogen receptor; FAC, fluorouracil, doxorubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; RR, risk ratio

[1] *Intervention: 32% of Albert 2011 received first 4 cycles of chemotherapy prior to surgery*

[2] *Control: 39% of control arm received CMF chemotherapy and arms were not otherwise equivalent*

[3] *Cannot judge imprecision as the number of people in subgroup and events are not reported*

[4] *High attrition in GEICAM 2003/02*

[5] *<300 events*

[6] *95% confidence interval crosses boundary for no effect (1) and minimally important difference (0.8) based on GRADE default value*

[7] *Significant heterogeneity - I2 77%; cannot be explored as no data was reported for subgroups of interest*

[8] *95% confidence interval crosses boundary for no effect (1) and both minimally important difference (0.8 and 1.25) based on GRADE default values*

[9] *Significant heterogeneity - I2 77%; cannot be explored as no data was reported for subgroups of interest*

[10] *Control: 39% of control arm in TACT received CMF chemotherapy and arms were not otherwise equivalent*

[11] *<300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important difference (0.8) based on GRADE default value*

[12] *<300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values*

[13] *Significant heterogeneity - I2 89%; explored in subgroup analysis*

[14] *Significant heterogeneity - I2 80%; explored in subgroup analysis*

[15] *Significant heterogeneity - I2 86%; cannot be explored as no data was reported for subgroups of interest*

[16] *Significant heterogeneity - I2 77%; explored in subgroup analysis*

[17] *Significant heterogeneity - I2 83%; cannot be explored as no data was reported for subgroups of interest*

[18] *Significant heterogeneity - I2 80%; cannot be explored as no data was reported for subgroups of interest*

Table 18: Clinical evidence profile: Comparison 4. AC/EC + paclitaxel/docetaxel versus AC/EC

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AC/EC + paclitaxel/docetaxel	AC/EC	Relative (95% CI)	Absolute		
DFS - All node positive (2 to 5.8 year follow-up)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	992/3502 (28.3%)	1130/3478 (32.5%)	HR 0.84 (0.77 to 0.91)	44 fewer per 1000 (from 24 fewer to 64 fewer)	HIGH	CRITICAL
DFS - T1; node positive (5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	0/159 (0%)	0/146 (0%)	HR 1.11 (0.67 to 1.83)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - T2/3; node positive (5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	0/216 (0%)	0/227 (0%)	HR 0.95 (0.68 to 1.33)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - ER+; node positive (5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	-	-	HR 1.14 (0.8 to 1.62)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - ER-; node positive (5.3 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AC/EC + paclitaxel/docetaxel	AC/EC	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	-	-	HR 0.72 (0.45 to 1.15)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - HER2+; node positive (5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	0/45 (0%)	0/49 (0%)	HR 1.08 (0.57 to 2.05)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - HER2-; node positive (5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	0/120 (0%)	0/118 (0%)	HR 1.38 (0.83 to 2.29)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - Mixed population (2 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	857/3146 (27.2%)	958/3134 (30.6%)	HR 0.85 (0.77 to 0.94)	39 fewer per 1000 (from 15 fewer to 61 fewer)	HIGH	CRITICAL
OS - Node positive (5.3 year follow-up)												
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Serious[2]	None	39/376 (10.4%)	43/374 (11.5%)	HR 0.84 (0.54 to 1.31)	17 fewer per 1000 (from 51	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AC/EC + paclitaxel/docetaxel	AC/EC	Relative (95% CI)	Absolute		
		risk of bias								fewer to 33 more)		
Treatment-related morbidity – nausea (2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	19/25 (76%)	15/25 (60%)	RR 1.27 (0.86 to 1.87)	162 more per 1000 (from 84 fewer to 522 more)	MODERATE	CRITICAL
Treatment-related morbidity - vomiting (2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	23/25 (92%)	24/25 (96%)	RR 0.96 (0.83 to 1.1)	38 fewer per 1000 (from 163 fewer to 96 more)	MODERATE	CRITICAL
Treatment-related morbidity - nausea/vomiting (5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	21/363 (5.8%)	21/354 (5.9%)	RR 0.98 (0.54 to 1.75)	1 fewer per 1000 (from 27 fewer to 44 more)	LOW	CRITICAL
Treatment-related morbidity – diarrhoea (2 to 5.3 year follow-up)												
2	Randomised trials	No serious risk of bias	Serious[5]	No serious indirectness	Very serious[4]	None	28/388 (7.2%)	9/379 (2.4%)	RR 3.91 (0.58 to 26.45)	69 more per 1000 (from 10 fewer to 604 more)	VERY LOW	CRITICAL
Treatment-related morbidity - diarrhoea - AC + paclitaxel vs. AC (2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	16/25 (64%)	8/25 (32%)	RR 2 (1.05 to 3.8)	320 more per 1000 (from 16 more to 896 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AC/EC + paclitaxel/docetaxel	AC/EC	Relative (95% CI)	Absolute		
Treatment-related morbidity - diarrhoea - EC + docetaxel vs. EC (5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	12/363 (3.3%)	1/354 (0.3%)	RR 11.7 (1.53 to 89.53)	30 more per 1000 (from 1 more to 250 more)	MODERATE	CRITICAL
Treatment-related morbidity – anaemia (2 to 5.3 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	16/388 (4.1%)	27/379 (7.1%)	RR 0.56 (0.34 to 0.92)	31 fewer per 1000 (from 6 fewer to 47 fewer)	MODERATE	CRITICAL
Treatment-related morbidity – leukopenia (2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	9/25 (36%)	12/25 (48%)	RR 0.75 (0.39 to 1.46)	120 fewer per 1000 (from 293 fewer to 221 more)	LOW	CRITICAL
Treatment-related morbidity – thrombocytopenia (2 to 5.3 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	4/388 (1%)	2/379 (0.5%)	RR 1.95 (0.36 to 10.58)	5 more per 1000 (from 3 fewer to 51 more)	LOW	CRITICAL
Treatment-related morbidity – neurotoxicity (2 to 5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	15/388 (3.9%)	0/379 (0%)	RR 13.32 (1.75 to 101.15)	-	MODERATE	CRITICAL
Treatment-related morbidity – neutropenia (5.3 year follow-up)												
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	233/363 (64.2%)	192/354 (54.2%)	RR 1.18 (1.05 to 1.34)	98 more per 1000 (from 27 more to	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AC/EC + paclitaxel/docetaxel	AC/EC	Relative (95% CI)	Absolute		
		risk of bias								184 more)		
Treatment-related morbidity - neutropenic fever (5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	24/363 (6.6%)	10/354 (2.8%)	RR 2.34 (1.14 to 4.82)	38 more per 1000 (from 4 more to 108 more)	MODERATE	CRITICAL
Treatment-related morbidity – hypersensitivity (5.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	19/363 (5.2%)	1/354 (0.28%)	RR 18.53 (2.49 to 137.67)	50 more per 1000 (from 4 more to 386 more)	MODERATE	CRITICAL
Treatment-related mortality (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	2/243 (0.82%)	5/255 (2%)	RR 0.42 (0.08 to 2.14)	11 fewer per 1000 (from 18 fewer to 22 more)	LOW	IMPORTANT

AC, doxorubicin, cyclophosphamide; CI, confidence interval; DFS, disease-free survival; EC, epirubicin, cyclophosphamide; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; RR, risk ratio

[1] Cannot judge imprecision as number of events not reported

[2] <300 events

[3] 95% confidence interval crosses boundary for no effect (1) and minimally important difference 1.25) based on GRADE default value

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

[5] Significant heterogeneity - I2 71%; explored in subgroup analysis

Table 19: Clinical evidence profile: Comparison 5. Epirubicin + docetaxel/paclitaxel versus FEC

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel/paclitaxel	FEC	Relative (95% CI)	Absolute		
DFS - Mixed population (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	273/535 (51%)	255/520 (49%)	HR 1.05 (0.89 to 1.25)	17 more per 1000 (from 39 fewer to 79 more)	HIGH	CRITICAL
OS - Mixed population (10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	230/2030 (11.3%)	226/2035 (11.1%)	HR 0.97 (0.81 to 1.17)	3 fewer per 1000 (from 20 fewer to 18 more)	HIGH	CRITICAL
OS - T1/2; node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	0/501 (0%)	0/490 (0%)	HR 0.88 (0.69 to 1.12)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - T3/4; node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	0/31 (0%)	0/29 (0%)	HR 0.87 (0.34 to 2.21)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - Age <60; node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	0/386 (0%)	0/349 (0%)	HR 0.84 (0.63 to 1.12)	-	number of events was not reported - insufficient	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel/paclitaxel	FEC	Relative (95% CI)	Absolute	Quality	Importance
											information to judge imprecision, and therefore overall quality	
OS - Age 60+; node positive (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	0/149 (0%)	0/171 (0%)	OR 0.91 (0.62 to 1.33)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Treatment-related morbidity – anaemia (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/516 (0.19%)	0/500 (0%)	RR 2.91 (0.12 to 71.2)	-	LOW	CRITICAL
Treatment-related morbidity – leukopenia (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	91/516 (17.6%)	86/500 (17.2%)	RR 1.03 (0.78 to 1.34)	5 more per 1000 (from 38 fewer to 58 more)	LOW	CRITICAL
Treatment-related morbidity – neutropenia (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	11/516 (2.1%)	15/500 (3%)	RR 0.71 (0.33 to 1.53)	9 fewer per 1000 (from 20 fewer to 16 more)	LOW	CRITICAL
Treatment-related morbidity - febrile neutropenia (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	0/516 (0%)	0/500 (0%)	-	-	number of events was not reported - insufficient information to	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel/paclitaxel	FEC	Relative (95% CI)	Absolute		
											judge imprecision, and therefore overall quality	
Treatment-related morbidity – thrombocytopenia (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	4/516 (0.78%)	13/500 (2.6%)	RR 0.3 (0.1 to 0.91)	18 fewer per 1000 (from 2 fewer to 23 fewer)	MODERATE	CRITICAL
Treatment-related morbidity – lymphoma (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	0/516 (0%)	1/500 (0.2%)	RR 0.32 (0.01 to 7.91)	1 fewer per 1000 (from 2 fewer to 14 more)	LOW	CRITICAL
Treatment-related morbidity - acute leukaemia (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	1/516 (0.19%)	0/500 (0%)	RR 2.91 (0.12 to 71.2)	-	LOW	CRITICAL
Treatment-related morbidity - nausea/vomiting (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	21/516 (4.1%)	39/500 (7.8%)	RR 0.52 (0.31 to 0.87)	37 fewer per 1000 (from 10 fewer to 54 fewer)	MODERATE	CRITICAL
Treatment-related morbidity – diarrhoea (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/516 (0.19%)	2/500 (0.4%)	RR 0.48 (0.04 to 5.33)	2 fewer per 1000 (from 4 fewer to 17 more)	LOW	CRITICAL
Treatment-related morbidity – hypersensitivity (10 year follow-up)												
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Very serious[2]	None	3/516 (0.58%)	1/500 (0.2%)	RR 2.91 (0.3 to 27.85)	4 more per 1000 (from 1	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel/paclitaxel	FEC	Relative (95% CI)	Absolute		
		risk of bias								fewer to 54 more)		
Treatment-related morbidity – neurological (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	4/516 (0.78%)	0/500 (0%)	RR 8.72 (0.47 to 161.57)	-	LOW	CRITICAL
Adequate dose intensity - dose reductions and/or treatment delays												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	94/535 (17.6%)	117/520 (22.5%)	RR 0.78 (0.61 to 1)	50 fewer per 1000 (from 88 fewer to 0 more)	MODERATE	IMPORTANT

CI, confidence interval; DFS, disease-free survival; FEC, fluorouracil, epirubicin, cyclophosphamide; HR, hazard ratio; OS, overall survival
[1] Cannot determine imprecision as number of events are not reported
[2] <300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values
[3] <300 events; imprecision cannot be determined as no events in either arm
[4] <300 events

Table 20: Clinical evidence profile: Comparison 6. Doxorubicin + docetaxel versus AC

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EC + docetaxel	FEC	Relative (95% CI)	Absolute		
OS (follow-up not reported)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	184/1787 (10.3%)	194/1792 (10.8%)	-	108 fewer per 1000 (from 108 fewer to 108 fewer)	HIGH	CRITICAL
Treatment-related morbidity - febrile neutropenia (2 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EC + docetaxel	FEC	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	126/311 (40.5%)	22/316 (7%)	RR 5.82 (3.8 to 8.9)	336 more per 1000 (from 195 more to 550 more)	MODERATE	CRITICAL
Treatment-related morbidity - nausea/vomiting (2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	17/311 (5.5%)	30/316 (9.5%)	RR 0.58 (0.32 to 1.02)	40 fewer per 1000 (from 65 fewer to 2 more)	LOW	CRITICAL
Treatment-related morbidity – diarrhoea (2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	9/311 (2.9%)	2/316 (0.63%)	RR 4.57 (1 to 20.99)	23 more per 1000 (from 0 more to 127 more)	MODERATE	CRITICAL

CI, confidence interval; EC, epirubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; OS, overall survival; RR, risk ratio

[1] <300 events

[2] <300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important difference (0.8) based on GRADE default value

Table 21: Clinical evidence profile: Comparison 7. Epirubicin + docetaxel versus epirubicin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel	Epirubicin	Relative (95% CI)	Absolute		
DFS - All node positive (5.4 year follow-up)												
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Serious[1]	None	84/406 (20.7%)	114/397 (28.7%)	HR 0.68 (0.51 to 0.9)	82 fewer per 1000 (from 25	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel	Epirubicin	Relative (95% CI)	Absolute		
		risk of bias								fewer to 129 fewer)		
DFS - ER+; node positive (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/313 (0%)	0/309 (0%)	HR 0.7 (0.49 to 1)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - ER-; node positive (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/82 (0%)	0/75 (0%)	HR 0.61 (0.38 to 0.99)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - T1; node positive (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/172 (0%)	0/184 (0%)	HR 0.51 (0.31 to 0.84)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - T2; node positive (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[2]	None	0/206 (0%)	0/186 (0%)	HR 0.76 (0.52 to 1.11)	-	Number of events was not reported - insufficient information to	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel	Epirubicin	Relative (95% CI)	Absolute	Quality	Importance
											judge imprecision, and therefore overall quality	
DFS - T3/4 (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias		No serious indirectness	[2]	None	0/27 (0%)	0/24 (0%)	HR 0.94 (0.36 to 2.45)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
OS - All node positive (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	52/406 (12.8%)	75/397 (18.9%)	HR 0.66 (0.46 to 0.94)	60 fewer per 1000 (from 10 fewer to 97 fewer)	HIGH	CRITICAL
Treatment-related morbidity – anaemia (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	126/396 (31.8%)	125/377 (33.2%)	RR 0.96 (0.78 to 1.18)	13 fewer per 1000 (from 73 fewer to 60 more)	MODERATE	CRITICAL
Treatment-related morbidity - acute myeloid leukaemia (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	0/396 (0%)	1/377 (0.27%)	RR 0.32 (0.01 to 7.77)	2 fewer per 1000 (from 3 fewer to 18 more)	LOW	CRITICAL
Treatment-related morbidity - febrile neutropenia (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	51/396 (12.9%)	7/377 (1.9%)	RR 6.94 (3.19 to 15.09)	110 more per 1000 (from 41 more to	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel	Epirubicin	Relative (95% CI)	Absolute		
										262 more)		
Treatment-related morbidity – leukopenia (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[5]	None	99/396 (25%)	83/377 (22%)	RR 1.14 (0.88 to 1.47)	31 more per 1000 (from 26 fewer to 103 more)	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Treatment-related morbidity – neutropenia (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	54/396 (13.6%)	54/377 (14.3%)	RR 0.95 (0.67 to 1.35)	7 fewer per 1000 (from 47 fewer to 50 more)	LOW	CRITICAL
Treatment-related morbidity – thrombocytopenia (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	1/396 (0.25%)	3/377 (0.8%)	RR 0.32 (0.03 to 3.04)	5 fewer per 1000 (from 8 fewer to 16 more)	LOW	CRITICAL
Treatment-related morbidity – diarrhoea (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	70/396 (17.7%)	21/377 (5.6%)	RR 3.17 (1.99 to 5.06)	121 more per 1000 (from 55 more to 226 more)	MODERATE	CRITICAL
Treatment-related morbidity – lethargy (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	25/396 (6.3%)	15/377 (4%)	RR 1.59 (0.85 to 2.96)	23 more per 1000 (from 6 fewer to 78 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel	Epirubicin	Relative (95% CI)	Absolute		
Treatment-related morbidity - nausea/vomiting (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	179/396 (45.2%)	211/377 (56%)	RR 0.81 (0.7 to 0.93)	106 fewer per 1000 (from 39 fewer to 168 fewer)	HIGH	CRITICAL
Treatment-related morbidity - peripheral neuropathy (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	52/396 (13.1%)	8/377 (2.1%)	RR 6.19 (2.98 to 12.85)	110 more per 1000 (from 42 more to 251 more)	MODERATE	CRITICAL
Treatment-related morbidity - unspecified neurological (5.4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	67/396 (16.9%)	35/377 (9.3%)	RR 1.82 (1.24 to 2.67)	76 more per 1000 (from 22 more to 155 more)	MODERATE	CRITICAL
Adequate dose intensity - received 85% of planned dose intensity - Cycles 1-3												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	384/406 (94.6%)	365/397 (91.9%)	RR 1.03 (0.99 to 1.07)	28 more per 1000 (from 9 fewer to 64 more)	HIGH	IMPORTANT
Adequate dose intensity - received 85% of planned dose intensity - Cycles 4-6												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	309/406 (76.1%)	334/397 (84.1%)	RR 0.9 (0.84 to 0.97)	84 fewer per 1000 (from 25 fewer to 135 fewer)	HIGH	IMPORTANT
HRQoL - change in global health status from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel	Epirubicin	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	63	49	-	MD 0.25 higher (8.46 lower to 8.96 higher)	LOW	IMPORTANT
HRQoL - change in physical functioning from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[8]	None	65	49	-	MD 4.22 lower (8.36 to 0.08 lower)	VERY LOW	CRITICAL
HRQoL - change in role functioning from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[8]	None	65	49	-	MD 8.39 higher (3.82 lower to 20.6 higher)	VERY LOW	IMPORTANT
HRQoL - change in emotional functioning from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[8]	None	64	49	-	MD 4.89 higher (4.04 lower to 13.82 higher)	VERY LOW	IMPORTANT
HRQoL - change in cognitive functioning from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	64	49	-	MD 0.93 lower (10.92 lower to 9.06 higher)	LOW	IMPORTANT
HRQoL - change in social functioning from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	64	48	-	MD 5.56 higher (4.82 lower to	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Epirubicin + docetaxel	Epirubicin	Relative (95% CI)	Absolute		
										15.94 higher)		
HRQoL - change in fatigue from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	No serious imprecision	None	65	49	-	MD 3.16 lower (11.93 lower to 5.61 higher)	MODERATE	IMPORTANT
HRQoL - change in nausea and vomiting from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	No serious imprecision	None	65	49	-	MD 0.76 lower (7.1 lower to 5.58 higher)	MODERATE	IMPORTANT
HRQoL - change in diarrhoea from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[8]	None	63	49	-	MD 3.17 higher (5.59 lower to 11.93 higher)	VERY LOW	IMPORTANT
HRQoL - change in body image from baseline (as measured by EORTC QOL) (Better indicated by lower values) (5.4 year follow-up)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	58	45	-	MD 0.37 lower (10.32 lower to 9.58 higher)	LOW	IMPORTANT

CI, confidence interval; DFS, disease-free survival; ER, oestrogen receptor; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; HRQoL, health-related quality of life; MD, mean difference; OS, overall survival; QoL, quality of life; RR, risk ratio

[1] <300 events

[2] Cannot judge imprecision as number of events are not reported

[3] 95% confidence interval crosses boundary for no effect (1) and minimally important difference (0.8) based on GRADE default value

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

[5] <300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important difference (1.25) based on GRADE default value

[6] Risk of detection bias as subjective, patient-reported outcome

[7] *N<400*
[8] *N<400; 95% confidence interval crosses boundary of no effect (0) and minimally important difference based on GRADE default value (0.5xSD)*

Table 22: Clinical evidence profile: Comparison 8. Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF versus doxorubicin/epirubicin (± cyclophosphamide) + CMF

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF	Doxorubicin/epirubicin (± cyclophosphamide) + CMF	Relative (95% CI)	Absolute	Quality	Importance
DFS - Mixed population (6.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[1]	None	0/451 (0%)	0/453 (0%)	HR 0.73 (0.56 to 0.95)	-	Number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
DFS - All node positive (3.2 to 8 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	629/2027 (31%)	358/1076 (33.3%)	HR 0.89 (0.78 to 1.01)	30 fewer per 1000 (from 62 fewer to 3 more)	MODERATE	CRITICAL
DFS - ER+; node positive (8 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	134/469 (28.6%)	131/405 (32.3%)	HR 0.82 (0.63 to 1.06)	49 fewer per 1000 (from 105 fewer to 16 more)	LOW	CRITICAL
DFS - HER2+; node positive (8 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	18/52 (34.6%)	29/54 (53.7%)	HR 0.57 (0.29 to 1.14)	182 fewer per 1000 (from 337	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF	Doxorubicin/epirubicin (± cyclophosphamide) + CMF	Relative (95% CI)	Absolute		
										fewer to 47 more)		
DFS - Triple negative; node positive (8 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	28/83 (33.7%)	40/110 (36.4%)	HR 0.9 (0.53 to 1.53)	29 fewer per 1000 (from 151 fewer to 136 more)	LOW	CRITICAL
OS - Mixed population (follow-up not reported for one trial; 6.3 year follow-up for other trial)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	57/937 (6.1%)	85/939 (9.1%)	HR 0.72 (0.57 to 0.93)	24 fewer per 1000 (from 6 fewer to 38 fewer)	MODERATE	CRITICAL
OS - All node positive (3.2 to 8 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	381/2027 (18.8%)	222/1076 (20.6%)	HR 0.88 (0.75 to 1.04)	22 fewer per 1000 (from 47 fewer to 7 more)	MODERATE	CRITICAL
Treatment-related morbidity - febrile neutropenia (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	269/1919 (14%)	63/968 (6.5%)	RR 2.15 (1.66 to 2.8)	75 more per 1000 (from 43 more to 117 more)	MODERATE	CRITICAL
Treatment-related morbidity – neutropenia (3.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	48/108 (44.4%)	53/108 (49.1%)	RR 0.91 (0.68 to 1.2)	44 fewer per 1000 (from 157 fewer to 98 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF	Doxorubicin/epirubicin (± cyclophosphamide) + CMF	Relative (95% CI)	Absolute	Quality	Importance
Treatment-related morbidity – anaemia (3.2 to 5 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[5]	None	62/2027 (3.1%)	49/1076 (4.6%)	RR 1.14 (0.2 to 6.52)	6 more per 1000 (from 36 fewer to 251 more)	VERY LOW	CRITICAL
Treatment-related morbidity - anaemia - Doxorubicin + docetaxel + CMF vs. Doxorubicin (± cyclophosphamide) + CMF (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[3]	None	58/1919 (3%)	48/968 (5%)	RR 0.61 (0.42 to 0.89)	19 fewer per 1000 (from 5 fewer to 29 fewer)	VERY LOW	CRITICAL
Treatment-related morbidity - anaemia - Epirubicin + paclitaxel + CMF vs. Epirubicin + cyclophosphamide + CMF (3.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	4/108 (3.7%)	1/108 (0.9%)	RR 4 (0.45 to 35.21)	28 more per 1000 (from 5 fewer to 317 more)	LOW	CRITICAL
Treatment-related morbidity – thrombocytopenia (3.2 to 5 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	80/2027 (3.9%)	24/1076 (2.2%)	RR 1.67 (1.07 to 2.62)	15 more per 1000 (from 2 more to 36 more)	LOW	CRITICAL
Treatment-related morbidity – leukopenia (3.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	48/108 (44.4%)	52/108 (48.1%)	RR 0.92 (0.69 to 1.23)	39 fewer per 1000 (from 149 fewer to 111 more)	LOW	CRITICAL
Treatment-related morbidity – hypersensitivity (5 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF	Doxorubicin/epirubicin (± cyclophosphamide) + CMF	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	25/1919 (1.3%)	0/968 (0%)	RR 25.74 (1.57 to 422.33)	-	LOW	CRITICAL
Treatment-related morbidity - nausea/vomiting (3.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	7/108 (6.5%)	12/108 (11.1%)	RR 0.58 (0.24 to 1.43)	47 fewer per 1000 (from 84 fewer to 48 more)	LOW	CRITICAL
Treatment-related morbidity – diarrhoea (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	58/1919 (3%)	10/968 (1%)	RR 2.93 (1.5 to 5.7)	20 more per 1000 (from 5 more to 49 more)	LOW	CRITICAL
Treatment-related morbidity – neurosensory (3.2 to 5 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	12/2027 (0.6%)	0/1076 (0%)	RR 8.78 (1.15 to 67.31)	-	LOW	CRITICAL
Treatment-related morbidity – fatigue (3.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	8/108 (7.4%)	3/108 (2.8%)	RR 2.67 (0.73 to 9.78)	46 more per 1000 (from 7 fewer to 244 more)	LOW	CRITICAL
Treatment-related mortality (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	Very serious[5]	None	3/1919 (0.16%)	1/968 (0.1%)	RR 1.51 (0.16 to 14.53)	1 more per 1000 (from 1 fewer to 14 more)	VERY LOW	IMPORTANT
Adequate dose intensity - dose reductions												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxorubicin/epirubicin + docetaxel/paclitaxel + CMF	Doxorubicin/epirubicin (± cyclophosphamide) + CMF	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	431/1919 (22.5%)	169/968 (17.5%)	RR 1.29 (1.1 to 1.51)	51 more per 1000 (from 17 more to 89 more)	MODERATE	IMPORTANT

CI, confidence interval; CMF, cyclophosphamide, methotrexate, flouroruacil; DFS, disease-free survival; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; RR, risk ratio

[1] Cannot determine imprecision as number of events are not reported

[2] Control: the second control arm in BIG 02-98 included CMF chemotherapy and the arms were not otherwise equivalent

[3] <300 events

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

[5] <300 events; 95% confidence interval crosses both no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values

Appendix G – Economic evidence study selection

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

Appendix H – Economic evidence tables

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

No economic evidence was identified for this review question.

Appendix J – Health economic analysis: cost-effectiveness of adding taxanes to anthracycline based chemotherapy in the treatment of early and locally advanced breast cancer

Background

Adjuvant chemotherapy for early breast cancer is given after surgery to reduce local and distant disease recurrence. The addition of taxanes to anthracycline based chemotherapy has been shown to further reduce the risk of recurrence. However, there is a need to balance the benefits of the additional treatment against the potential increased morbidity as well as the cost of treatment. In the previous guideline CG80 (NICE 2009), the addition of taxanes was recommended only in node positive breast cancer. However, there is now evidence that the benefit of additional treatment may extend to other groups, such as those based on the phenotype of disease (for example ER- and HER2+ status).

Aim

To estimate the cost-effectiveness of adding taxanes to anthracycline based chemotherapy in the treatment of early and locally advanced breast cancer.

Methods

Existing economic evidence

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. No relevant economic studies were identified that were directly applicable.

De novo economic evaluation

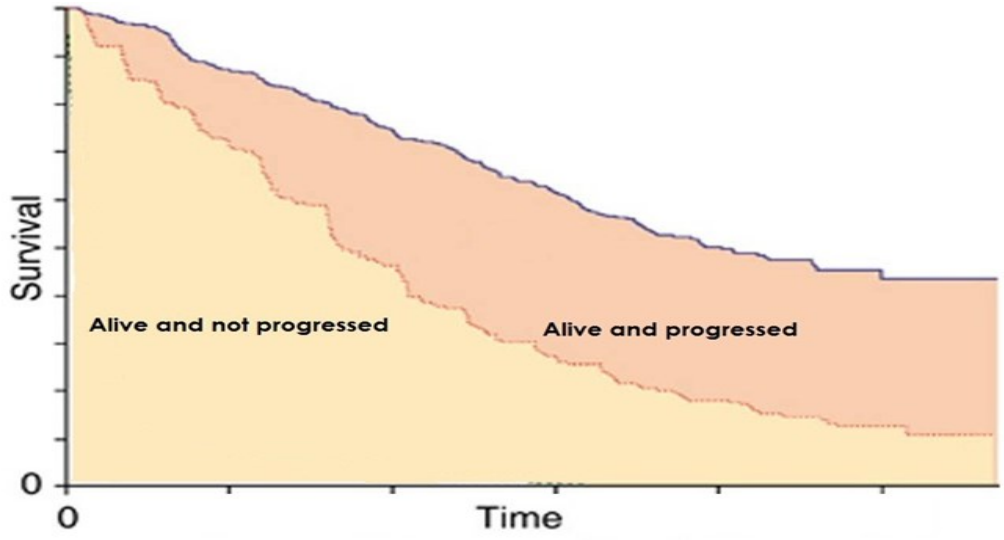
Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE reference case (see Developing NICE guidelines: the manual). The model considered a 50-year time horizon with future costs and benefits discounted at a rate of 3.5% (as recommended in the NICE reference case).

Clinical data and model approach

The economic analysis was based on OS and DFS estimates for each of the treatments included in the analysis. The analysis essentially took the form of a simple partitioned survival analysis (Figure 133), in which 3 mutually exclusive health states were derived from the OS and DFS estimates:

- alive without progressed disease
- alive with progressed disease
- dead

Figure 133: Illustrative example of partitioned survival analysis



Overall and disease free survival

Overall and disease-free survival for each of the interventions was estimated using data on absolute and relative risk from the systematic review of the clinical evidence conducted for this topic. Baseline absolute OS and DFS for patients receiving anthracycline based chemotherapy were taken from the anthracycline chemotherapy arms in each of the comparisons. OS and DFS estimates for each of the chemotherapy and taxane regimens were estimated by applying the relative treatment effect (using hazard ratios [HRs]) associated with each regimen to the absolute risk estimates. Table 23 to Table 30 show the OS and DFS estimates for the each of the populations considered in the analysis.

Table 23: Overall and disease free survival for people with node-positive breast cancer

Parameter	Overall survival		Disease-free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
EC+docetaxel versus FEC				
FEC	-	89.0% at 5 years	-	78.0% at 5 years
EC+docetaxel	0.81 (0.6 2-1.04)	91.1% at 5 years	0.92 (0.81-1.06)	79.8% at 5 years
TAC versus FAC				
FAC	-	69.0% at 10 years	-	82.0% at 10 years
TAC	0.74 (0.61-0.90)	77.1% at 6.4 years	0.74 (0.55-0.98)	86.7% at 6.4 years
FEC/FAC+taxane versus FEC/FAC				
FEC/FAC	-	79.0% at 5 years	-	66.0% at 5 years
FEC/FAC+taxane	0.79 (0.68-0.93)	83.4% at 5 years	0.92 (0.84-1.01)	68.7% at 5 years
AC/EC+taxane versus AC/EC				

Parameter	Overall survival		Disease-free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
AC/EC	-	89.0% at 5.3 years	-	56.0% at 2 years
AC/EC+taxane	0.84 (0.53-1.31)	90.8% at 5.3 years	0.84 (0.77-0.91)	63.0% at 2 years
Epirubicin+docetaxel versus epirubicin				
Epirubicin	-	81.0% at 5.4 years	-	71.0% at 5.4 years
Epirubicin+docetaxel	0.66 (0.46-0.94)	87.5% at 5.4 years	0.68 (0.51-0.90)	80.3% at 5.4 years
Doxorubicin/epirubicin+taxane+CMF versus doxorubicin/epirubicin+CMF				
Doxorubicin/epirubicin+CMF	-	80.0% at 3.2 years	-	65.0% at 3.2 years
Doxorubicin/epirubicin+taxane	0.88 (0.75-1.04)	82.4% at 3.2 years	0.89 (0.78-1.01)	68.9% at 3.2 years

Table 24: Overall and disease free survival for people with node-negative breast cancer

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
TAC versus FAC				
FAC	-	93.0% at 6.4 years	-	82.0% at 6.4 years
TAC	0.76 (0.45-1.27)	94.7% at 6.4 years	0.74 (0.55-0.98)	86.7% at 6.4 years
FEC/FAC+taxane versus FEC/FAC				
FEC/FAC	-	96.0% at 5 years	-	90.0% at 5 years
FEC/FAC+taxane	0.79 (0.68-1.27)	96.8% at 5 years	0.79 (0.62-0.99)	92.1% at 5 years

Table 25: Overall and disease free survival for people with triple negative breast cancer

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
EC+docetaxel versus FEC				
FEC	-	89.0% at 5 years	-	53.5% at 5 years
EC+docetaxel	0.81 (0.62-1.04)	91.1% at 5 years	0.87 (0.57-1.34)	59.5% at 5 years
TAC versus FAC				
FAC	-	69.0% at 10 years	-	58.6% at 6.4 years

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
TAC	0.81 (0.51-1.28)	74.9% at 10 years	0.84 (0.56-1.25)	65.2% at 6.4 years
FEC/FAC+taxane versus FEC/FAC				
FEC/FAC	-	79.0% at 5 years	-	58.6%* at 5 years
FEC/FAC+taxane	0.88 (0.49-1.58)	81.5% at 5 years	NR	64.0%* at 5 years
Doxorubicin/epirubicin+taxane+CMF versus doxorubicin/epirubicin+CMF				
Doxorubicin/epirubicin+CMF	-	80.0% at 3.2 years	-	63.6% at 8 years
Doxorubicin/epirubicin+taxane	0.88 (0.75-1.04)	82.4% at 3.2 years	0.90 (0.53-1.53)	67.3% at 8 years

**Assumption since no value was reported in the clinical evidence review. Estimated as the average of the absolute values in the chemotherapy and taxane arms in the other comparisons*.

Table 26: Overall and disease free survival for people with HER2-positive breast cancer

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
EC+docetaxel versus FEC				
FEC	-	89.0% at 5 years	-	65.0% at 5 years
EC+docetaxel	0.81 (0.62-1.04)	91.1% at 5 years	1.16 (0.8-1.69)	59.4% at 5 years
TAC versus FAC				
FAC 10yr OS 6.4yr DFS	-	69.0% at 10 years	-	55.5% at 6.4 years
TAC	0.63 (0.43-0.93)	80.5% at 10 years	0.60 (0.43-0..83)	73.3% at 6.4 years
FEC/FAC+taxane versus FEC/FAC				
FEC/FAC	-	79.0% at 5 years	-	55.5%* at 5 years
FEC/FAC+taxane	0.50 (0.27-0.91)	89.5% at 5 years	NR	63.5%* at 5 years
AC/EC+taxane versus AC/EC				
AC/EC 5.3yr OS 2yr DFS	-	89.0% at 5.3 years	-	55.5% at 2 years
AC/EC+taxane	0.84 (0.54-1.31)	90.8% at 5.3 years	1.08 (0.57-2.05)	51.9% at 2 years
Doxorubicin/epirubicin+taxane+CMF versus doxorubicin/epirubicin+CMF				
Doxorubicin/epirubicin+CMF 3.2yr OS 3.2yr DFS	-	80.0% at 3.2 years	-	46.0% at 3.2 years
Doxorubicin/epirubicin+taxane	0.88 (0.75-1.04)	82.4% at 3.2 years	0.57 (0.29-1.14)	69.2% at 3.2 years

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute

**Assumption since no value was reported in the clinical evidence review. Estimated as the average of the absolute values in the chemotherapy and taxane arms in the other comparisons.*

Table 27: Overall and disease free survival for people with HER2-negative breast cancer

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
EC+docetaxel versus FEC				
FEC	-	89.0% at 5 years	-	73.0% at 5 years
EC+docetaxel	0.81 (0.62-1.04)	91.1% at 5 years	1.06 (0.83-1.35)	71.4% at 5 years
TAC versus FAC				
FAC	-	69.0% at 10 years	-	73.0% at 6.4 years
TAC	0.81 (0.64-1.02)	74.9% at 10 years	0.90 (0.74-1.10)	75.7% at 6.4 years
FEC/FAC+taxane versus FEC/FAC				
FEC/FAC	-	79.0% at 5 years	-	73.0%* at 5 years
FEC/FAC+taxane	1.32 (0.98-1.76)	72.3% at 5 years	NR	69.9%* at 5 years
AC/EC+taxane versus AC/EC				
AC/EC	-	89.0% at 5.3 years	-	73.0% at 2 years
AC/EC+taxane	0.84 (0.54-1.31)	90.8% at 5.3 years	1.38 (0.83-2.29)	62.7% at 2 years

**Assumption since no value was reported in the clinical evidence review. Estimated as the average of the absolute values in the chemotherapy and taxane arms in the other comparisons.*

Table 28: Overall and disease free survival for people with ER-positive breast cancer

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
EC+docetaxel versus FEC				
FEC	-	89.0% at 5 years	-	68.0% at 8 years
EC+docetaxel	0.81 (0.62-1.04)	91.1% at 5 years	0.52 (0.26-1.04)	83.4% at 8 years
FEC/FAC+taxane versus FEC/FAC				
FEC/FAC	-	79.0% at 5 years	-	68.0%* at 8 years
FEC/FAC+taxane	0.79 (0.62-1.01)	83.4% at 5 years	NR	73.5%* at 8 years
AC/EC+taxane versus AC/EC				

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
AC/EC	-	89.0% at 5.3 years	-	68.0% at 8 years
AC/EC+taxane	0.84 (0.54-1.31)	90.8% at 5.3 years	1.14 (0.8-1.62)	63.5% at 8 years
Doxorubicin/epirubicin+taxane+CMF versus doxorubicin/epirubicin+CMF				
Doxorubicin/epirubicin+CMF	-	80.0% at 3.2 years	-	68.0% at 8 years
Doxorubicin/epirubicin+taxane	0.88 (0.75-1.04)	82.4% at 3.2 years	0.82 (0.63-1.06)	73.8% at 8 years

**Assumption since no value was reported in the clinical evidence review. Estimated as the average of the absolute values in the chemotherapy and taxane arms in the other comparisons.*

Table 29: Overall and disease free survival for people with ER-negative breast cancer

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
EC+docetaxel versus FEC				
FEC	-	89.0% at 5 years	-	78.0% at 8 years
EC+docetaxel	0.81 (0.62-1.04)	91.1% at 5 years	0.49 (0.22-1.08)	89.2% at 8 years
FEC/FAC+taxane versus FEC/FAC				
FEC/FAC	-	79.0% at 5 years	-	66.0% at 8 years
FEC/FAC+taxane	0.72 (0.50-1.03)	84.9% at 5 years	0.92 (0.84-1.01)	68.7% at 8 years
AC/EC+taxane versus AC/EC				
AC/EC	-	89.0% at 5.3 years	-	56.0% at 8 years
AC/EC+taxane	0.84 (0.54-1.31)	90.8% at 5.3 years	0.72 (0.45-1.15)	68.3% at 8 years

Table 30: Overall and disease free survival for 'mixed' population

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
FEC/FAC+taxane versus FEC/FAC				
FEC/FAC	-	85.0% at 5 years	-	74.0% at 5 years
FEC/FAC+taxane	0.90 (0.8-1.01)	86.5% at 5 years	0.72 (0.61-0.86)	81.3% at 5 years
Epirubicin+taxane versus FEC				
Epirubicin	-	73.0% at 10 years	-	51.0% at 10 years

Parameter	Overall survival		Disease free survival	
	Mortality HR (95% CI)	Absolute	Recurrence HR (95% CI)	Absolute
Epirubicin+docetaxel	0.97 (0.81-1.17)	73.8% at 10 years	1.05 (0.89-1.25)	48.6% at 10 years
Doxorubicin/epirubicin+taxane+CMF versus doxorubicin/epirubicin+CMF				
Doxorubicin/epirubicin+CMF	-	83.0% at 3.2 years	-	62.5% at 3.2 years
Doxorubicin/epirubicin+taxane	0.72 (0.57-0.93)	87.8% at 3.2 years	0.73 (0.56-0.95)	72.6% at 3.2 years

A simple exponential function was used to estimate overall and disease free survival based on the values at the longest time points reported in each of the studies (shown in the tables above). This approach allows for survival estimates to be extrapolated beyond the time period covered in the studies and up to the modelled time horizon of 50 years. Since it is not known whether the treatment effect with taxanes would endure beyond the time period covered in the studies, it was assumed that that there would be no treatment effect beyond this point. This follows the conservative approach which has generally been adopted in the analysis whereby, in areas of uncertainty requiring assumptions to be made, we aimed to bias against the intervention and not in favour of it. Alternative treatment effect durations are explored in sensitivity analysis (including a scenario where a lifetime treatment effect duration is assumed).

Mortality from causes other than breast cancer was captured using 2013-2015 life tables for England and Wales from the Office of National Statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. A starting age of 49 years was applied in the model based on the average age reported in Piccart-Gebhart 2005. The other cause mortality estimates were used in conjunction with the overall survival estimates above to estimate the proportion of people that died of disease-specific and other causes.

Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS and PSS were included. Where possible, all costs were estimated in 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate healthcare resource group (HRG) code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) combined with dosage information from the British National Formulary (BNF). Where costs were not available from eMit, list prices from the BNF were used. Other resource use and cost information was sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the committee.

Chemotherapy costs

Table 31 details the cost of each chemotherapy regimen included in the model. The chemotherapy delivery costs were sourced from NHS Reference Costs 2015/16 and drug costs were sourced from eMit.

Table 31: Estimated chemotherapy costs per cycle

Treatment	Cost	Source
5-Fluorouracil, epirubicin and cyclophosphamide (FEC)		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
5-Fluorouracil 500 mg/m^2 on day one	£1.26	eMit
Epirubicin 75 mg/m^2 on day one	£18.97	eMit
Cyclophosphamide 500 mg/m^2 on day one	£7.84	eMit
Cost per cycle	**£281.39**	
Total cost for six cycles	**£1,688.34**	
5-Fluorouracil, doxorubicin and cyclophosphamide (FAC)		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
5-Fluorouracil 500 mg/m^2 on day one	£1.26	eMit
Doxorubicin 50 mg/m^2 on day one	£10.16	eMit
Cyclophosphamide 500 mg/m^2 on day one	£7.84	eMit
Cost per cycle	**£272.58**	
Total cost for six cycles	**£1,635.48**	
Docetaxel, doxorubicin and cyclophosphamide (TAC)		
Deliver more complex parenteral chemotherapy	£336.57	NHS Reference costs 2015/16 – day case
Docetaxel 75 mg/m^2 on day one	£20.62	eMit
Doxorubicin 50 mg/m^2 on day one	£10.16	eMit
Cyclophosphamide 500 mg/m^2 on day one	£7.84	eMit
Cost per cycle	**£375.19**	
Total cost for six cycles	**£2,251.14**	
5-Fluorouracil, epirubicin, cyclophosphamide and docetaxel (FEC-TH)		
Cycles 1-3		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
5-Fluorouracil 500 mg/m^2 on day one	£1.26	eMit
Epirubicin 100 mg/m^2 on day one	£25.23	eMit
Cyclophosphamide 500 mg/m^2 on day one	£7.84	eMit
Cost per cycle	**£287.65**	
Cycles 4-6		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Dexamethasone 8 mg oral twice daily for three days	£15.67	eMit
Doxorubicin 50 mg/m^2 on day one	£10.16	eMit
Docetaxel 100 mg/m^2 on day one	£7.84	eMit
Cost per cycle	**£293.28**	
Total cost for six cycles	**£1,742.79**	
5-Fluorouracil, epirubicin, cyclophosphamide and paclitaxel (FEC-PH)		
Cycles 1-3		

Treatment	Cost	Source
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
5-Fluorouracil 500 mg/m^2 on day one	£1.26	eMit
Epirubicin 100 mg/m^2 on day one	£25.23	eMit
Cyclophosphamide 500 mg/m^2 on day one	£7.84	eMit
Cost per cycle	**£287.65**	
Cycles 4-7		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Deliver subsequent elements of a chemotherapy cycle	£361.04	NHS Reference costs 2015/16 – day case
Paclitaxel 80 mg/m^2 on day one, eight and fifteen	£37.65	eMit
Cost per cycle	**£652.01**	
Total cost for seven cycles	**£3,471.00**	
Doxorubicin and cyclophosphamide (AC)		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Doxorubicin 60 mg/m^2 on day one	£9.61	eMit
Cyclophosphamide 600 mg/m^2 on day one	£16.71	eMit
Cost per cycle	**£279.64**	
Total cost for six cycles	**£1,677.86**	
Epirubicin and cyclophosphamide (EC)		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Epirubicin 75 mg/m^2 on day one	£18.97	eMit
Cyclophosphamide 600 mg/m^2 on day one	£16.71	eMit
Cost per cycle	**£289.00**	
Total cost for six cycles	**£1,734.02**	
AC and docetaxel		
Cycles 1-3		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Doxorubicin 60 mg/m2 on day one	£9.61	eMit
Cyclophosphamide 600 mg/m^2 on day one	£16.71	eMit
Cost per cycle	**£279.64**	
Cycles 4-6		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Dexamethasone 8 mg oral twice daily for three days	£15.67	eMit
Docetaxel 100 mg/m^2 on day one	£24.29	eMit
Cost per cycle	**£293.28**	
Total cost for six cycles	**£1,718.77**	
AC and paclitaxel		
Cycles 1-3		

Treatment	Cost	Source
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Doxorubicin 60 mg/m^2 on day one	£9.61	eMit
Cyclophosphamide 600 mg/m^2 on day one	£16.71	eMit
Cost per cycle	**£279.64**	
Cycles 4-7		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Deliver subsequent elements of a chemotherapy cycle	£361.04	NHS Reference costs 2015/16 – day case
Paclitaxel 80 mg/m^2 on day one, eight and fifteen	£37.65	eMit
Cost per cycle	**£652.01**	
Total cost for seven cycles	**£3,446.97**	
EC and docetaxel		
Cycles 1-3		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Epirubicin 75 mg/m^2 on day one	£18.97	eMit
Cyclophosphamide 600 mg/m^2 on day one	£16.71	eMit
Cost per cycle	**£289.00**	
Cycles 4-6		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Dexamethasone 8 mg oral twice daily for three days	£15.67	eMit
Docetaxel 100 mg/m^2 on day one	£24.29	eMit
Cost per cycle	**£293.28**	
Total cost for six cycles	**£1,746.85**	
EC and docetaxel		
Cycles 1-3		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Epirubicin 75 mg/m^2 on day one	£18.97	eMit
Cyclophosphamide 600 mg/m^2 on day one	£16.71	eMit
Cost per cycle	**£289.00**	
Cycles 4-7		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Deliver subsequent elements of a chemotherapy cycle	£361.04	NHS Reference costs 2015/16 – day case
Paclitaxel 80 mg/m^2 on day one, eight and fifteen	£37.65	eMit
Cost per cycle	**£652.01**	
Total cost for seven cycles	**£3,475.05**	
Epirubicin		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case

Treatment	Cost	Source
Deliver subsequent elements of a chemotherapy cycle	£361.04	NHS Reference costs 2015/16 – day case
Epirubicin 50 mg/m^2 on day one and eight	£29.72	eMit
Cost per cycle	**£644.08**	
Total cost for six cycles	**£3,864.49**	
Epirubicin and taxane		
Cycles 1-3		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Deliver subsequent elements of a chemotherapy cycle	£361.04	NHS Reference costs 2015/16 – day case
Epirubicin 50 mg/m^2 on day one and eight	£29.72	eMit
Cost per cycle	**£644.08**	
Cycles 4-6		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Dexamethasone 8mg oral twice daily for three days	£15.67	eMit
Docetaxel 100 mg/m^2 on day one	£24.29	eMit
Cost per cycle	**£293.28**	
Total cost for six cycles	**£2,812.08**	
Doxorubicin and cyclophosphamide, methotrexate and 5-fluorouracil (CMF)		
Cycles 1-4		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Doxorubicin 75 mg/m2 on day one	£12.67	eMit
Cost per cycle	**£265.99**	
Cycles 5-7		
Deliver more complex parenteral chemotherapy	£336.57	NHS Reference costs 2015/16 – day case
Cyclophosphamide 600 mg/m^2 on day one and eight	£33.42	eMit
Methotrexate 40 mg/m^2 on day one and eight	£14.48	eMit
5-Fluorouracil 500 mg/m^2 on day one and eight	£10.16	eMit
Cost per cycle	**£394.63**	
Total cost for seven cycles	**£2,247.85**	
Doxorubicin and cyclophosphamide, methotrexate and 5-fluorouracil (CMF) plus taxane		
Cycles 1-3		
Deliver more complex parenteral chemotherapy	£336.57	NHS Reference costs 2015/16 – day case
Doxorubicin 50 mg/m^2 on day one	£12.67	eMit
Docetaxel 75 mg/m^2 on day one	£20.62	
Cost per cycle	**£367.35**	
Cycles 4-6		
Deliver more complex parenteral chemotherapy	£336.57	NHS Reference costs 2015/16 – day case
Cyclophosphamide 600 mg/m^2 on day one and eight	£33.42	eMit

Treatment	Cost	Source
Methotrexate 40 mg/m^2 on day one and eight	£14.48	eMit
5-Fluorouracil 500 mg/m^2 on day one and eight	£10.16	eMit
Cost per cycle	**£394.63**	
Total cost for seven cycles	**£2,653.29**	

Subsequent treatment costs

Subsequent treatment costs (following disease recurrence or progression) were estimated based on the treatment that would be most likely to be used (based on the estimation of the committee). It was assumed that treatment would vary depending upon the type of recurrence with data from the HERA trial used to estimate the proportion of recurrences that were locoregional (18%), regional (5%), contralateral (8%) and distant (69%).

It was assumed that people with locoregional, regional or contralateral recurrence would undergo a mastectomy if they originally had breast-conserving surgery (42% from Cameron 2017) or a 'major breast procedure' if they originally had a mastectomy (58% from Cameron 2017). It was also assumed that breast reconstruction would be performed (either at the time of mastectomy or delayed). It was further assumed that lymph node clearance would be performed for people with regional recurrence and that radiotherapy would be used if tumours were not previously treated with radiotherapy (24% from Cameron 2017); it was assumed that everyone would receive adjuvant chemotherapy, trastuzumab and peruzumab. It was assumed that people with distant recurrence would receive chemotherapy, trastuzumab and pertuzumab.

Table 32 to Table 35 detail the costs that were applied for each type of recurrence.

Table 32: Subsequent treatment costs for locoregional recurrence

Treatment	Proportion†	Cost	Source
Major breast procedures (in those people that originally had mastectomy)			
Unilateral Major Breast Procedures with CC Score 6+ (JA20D)	4%	£3,797	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 3-5 (JA20E)	17%	£3,265	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 0-2 (JA20F)	59%	£2,915	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Major Breast Procedures with CC Score 1+ (JA21A)	9%	£4,143	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Major Breast Procedures with CC Score 0 (JA21B)	10%	£3,834	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£3,219.70**	
Delayed breast reconstruction			
Unilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA30Z)	41%	£5,825	NHS Reference costs 2015/16 - Elective inpatient

Treatment	Proportion†	Cost	Source
Bilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA31Z)	11%	£5,799	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Delayed Free Perforator Flap Breast Reconstruction (JA34Z)	39%	£9,393	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Free Perforator Flap Breast Reconstruction (JA35Z)	10%	£11,145	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,736.86**	
Mastectomy with reconstruction (in people that originally had breast conserving surgery)			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA32Z)	54%	£5,883	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA33Z)	23%	£7,079	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA36Z)	16%	£10,627	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA37Z)	7%	£13,083	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,451.79**	
Radiotherapy			
Preparation for Complex Conformal Radiotherapy (SC51Z)	-	£654.57	NHS Reference costs 2015/16 - outpatient
Deliver a Fraction of Complex Treatment on a Megavoltage Machine (SC23Z)	-	£126.48	NHS Reference costs 2015/16 - outpatient
Number of fractions	-	20	Assumption
Total radiotherapy cost		**£3,184.15**	
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	**-**	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	**-**	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	**-**	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600 mg	**-**	£1,222.20	BNF
Pertuzumab cost for two 420 mg vials (loading dose)	**-**	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**

Treatment	Proportion†	Cost	Source
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600 mg	-	£1,222.20	BNF
Pertuzumab cost for 420 mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600 mg	-	£1,222.20	BNF
Pertuzumab cost for 420 mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

1 **Table 33: Subsequent treatment costs for regional recurrences**

Treatment	Proportion†	Cost	Source
Major breast procedures with lymph node clearance (for regional recurrences in people that originally had mastectomy)			
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 5+ (JA38A)	13%	£4,535	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 2-4 (JA38B)	38%	£3,814	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 0-1 (JA38C)	42%	£3,694	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Major Breast Procedures with Lymph Node Clearance (JA39Z)	7%	£5,522	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£3,971.97**	
Delayed breast reconstruction			
Unilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA30Z)	41%	£5,825	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA31Z)	11%	£5,799	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Delayed Free Perforator Flap Breast Reconstruction (JA34Z)	39%	£9,393	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Free Perforator Flap Breast Reconstruction (JA35Z)	10%	£11,145	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,736.86**	

Treatment	Proportion†	Cost	Source
Mastectomy with reconstruction (in people that originally had breast conserving surgery)			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA32Z)	54%	£5,883	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA33Z)	23%	£7,079	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA36Z)	16%	£10,627	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA37Z)	7%	£13,083	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,451.79**	
Radiotherapy			
Preparation for Complex Conformal Radiotherapy (SC51Z)	-	£654.57	NHS Reference costs 2015/16 - outpatient
Deliver a Fraction of Complex Treatment on a Megavoltage Machine (SC23Z)	-	£126.48	NHS Reference costs 2015/16 - outpatient
Number of fractions	-	20	Assumption
Total radiotherapy cost		**£3,184.15**	
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	**-**	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	**-**	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	**-**	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600 mg	**-**	£1,222.20	BNF
Pertuzumab cost for two 420 mg vials (loading dose)	**-**	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**
Deliver more complex parenteral chemotherapy	**-**	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	**-**	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600 mg	**-**	£1,222.20	BNF
Pertuzumab cost for 420 mg vial	**-**	£2,395.00	NICE TA and BNF
Total cost per cycle	**-**	***£3,988.17***	
Subsequent cycles (until disease progression)			

Treatment	Proportion†	Cost	Source
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600 mg	-	£1,222.20	BNF
Pertuzumab cost for 420 mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

1 **Table 34: Subsequent treatment costs for contralateral recurrence**

Treatment	Proportion†	Cost	Source
Major breast procedures (in people that originally had mastectomy)			
Unilateral Major Breast Procedures with CC Score 6+ (JA20D)	5%	£3,797	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 3-5 (JA20E)	21%	£3,265	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 0-2 (JA20F)	74%	£2,915	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£3,036.41**	
Delayed breast reconstruction			
Unilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA30Z)	51%	£5,825	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Delayed Free Perforator Flap Breast Reconstruction (JA34Z)	49%	£9,393	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,571.91**	
Mastectomy with reconstruction (in people that originally had breast conserving surgery)			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA32Z)	77%	£5,883	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA36Z)	23%	£10,627	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£6,973.11**	
Radiotherapy			
Preparation for Complex Conformal Radiotherapy (SC51Z)	-	£654.57	NHS Reference costs 2015/16 - outpatient
Deliver a Fraction of Complex Treatment on a Megavoltage Machine (SC23Z)	-	£126.48	NHS Reference costs 2015/16 - outpatient
Number of fractions	-	20	Assumption
Total radiotherapy cost		**£3,184.15**	
Adjuvant chemotherapy, trastuzumab and pertuzumab			

Treatment	Proportion†	Cost	Source
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	-	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600 mg	-	£1,222.20	BNF
Pertuzumab cost for two 420 mg vials (loading dose)	-	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600 mg	-	£1,222.20	BNF
Pertuzumab cost for 420 mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600 mg	-	£1,222.20	BNF
Pertuzumab cost for 420 mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

1 **Table 35: Subsequent treatment costs for distant recurrence**

Treatment	Proportion†	Cost	Source
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	-	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600 mg	-	£1,222.20	BNF
Pertuzumab cost for two 420 mg vials (loading dose)	-	£4,790.00	NICE TA and BNF

Treatment	Proportion†	Cost	Source
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600 mg	-	£1,222.20	BNF
Pertuzumab cost for 420 mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600 mg	-	£1,222.20	BNF
Pertuzumab cost for 420 mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

Cardiac event monitoring costs

Treatment with trastuzumab is associated with a risk of cardiotoxicity and therefore people receiving trastuzumab typically undergo cardiac monitoring. In clinical practice, echocardiograms are typically used for cardiac monitoring but in some cases multi-gated acquisition (MUGA) scans or cardiac MRI scans may be used.

In the model, a weighted average cost per scan was calculated using weightings estimated by the committee. It was assumed that 80% of scans would be echocardiograms, 10% would be MUGA scans and 10% would be cardiac MRI scans. The cost for each scan was sourced from NHS reference costs 2015/16. Reflecting clinical practice, it was assumed that people would undergo 5 cardiac monitoring scans in the year that they received trastuzumab.

Table 36 details the cost of cardiac event monitoring applied in the model.

Table 36: Cardiac event monitoring costs

Treatment	Proportion†	Cost	Source
Simple Echocardiogram, 19 years and over (RD51A)	80%	£72.00	NHS Reference Costs 2015/16 – outpatient
Multi Gated Acquisition (MUGA) Scan (RN22Z)	10%	£204.70	NHS Reference Costs 2015/16 – outpatient
Cardiac Magnetic Resonance Imaging Scan with pre and post contrast (RD10Z)	10%	£329.27	NHS Reference Costs 2015/16 – outpatient
Weighted average cost per scan		**£111.00**	
Average cost for five scans		**£554.99**	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs

Follow-up costs

The cost of post-treatment follow-up to detect disease recurrence was incorporated in the model. It was assumed that people would have clinical follow-up appointments every 3 to 6 months in years 1 to 3, every 6-12 months in years 4 and 5 and annually thereafter. The cost for each follow-up appointment was estimated to be £120.98 based on the cost of a 'consultant led, non-admitted face to face attendance, follow-up' from NHS Reference Costs 2015/16.

Palliative care costs

The cost of palliative care was estimated using data from a costing report by the Nuffield Trust (Georghiou 2014). A cost of £7,287 for 3 months was applied based on the average resource use of people with cancer in the last 3 months of life. Table 37 details the palliative care cost applied in the model.

Table 37: Estimated palliative care cost per person in the last three months of life

Type of care	Average cost per person	Source
Cost of all hospital contacts	£5,890	Exploring the cost of care at the end of life (Nuffield Trust, Georghiou 2014)
Local authority-funded care	£444	
District nursing care	£588	
GP contacts	£365	
Average palliative care cost per person	**£7,287**	

It should be noted that this cost is generic to all cancers and is not specifically related to breast cancer. However, in the absence of more robust data, it has been assumed that the costs in breast cancer would not differ substantially.

Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality-adjusted life years (QALYs). These are estimated by combining the life year estimates with utility values or quality of life (QoL) weights associated with being in a particular health state.

The QoL values applied in the model were sourced from Essers 2010, which reported utility values for people with HER2+ breast cancer and was applicable to the UK setting. This study was identified and used by the Evidence Review Group (ERG) in their revised economic analysis as part of the technology appraisal (TA) for pertuzumab in neoadjuvant treatment of HER2-positive breast cancer (NICE TA424).

Table 38 details the QoL values applied in the analysis. People in the 'disease free' health state would have a QoL value of 0.847 which would decrease to 0.810 in people with a recurrence. The QoL value for metastatic disease was applied to people in the last year of life before dying of cancer-specific mortality.

Table 38: Health-related quality of life values

Health state	Value	Source
Event free or remission	0.847	Essers 2010
Recurrence	0.810	Essers 2010
Metastases	0.484	Essers 2010

Results

Base-case results

The base-case results of each of the analyses for the overall population and subgroups are shown in Table 39 to Table 46. When interpreting the results of the deterministic analysis, it is important to remember that many of the differences in clinical effectiveness that have been modelled were not statistically significant. This limits the reliability of the base case estimates.

In people with node-positive disease it can be seen that the addition of taxanes to chemotherapy was cost-effective in all comparisons. In some cases, the addition of taxanes was found to increase costs and effectiveness with a resulting ICER value lower than the NICE threshold of £20,000 per QALY while in other cases it was found to reduce costs as well as improve effectiveness (therefore it was found to be dominant). The average result showed the addition of taxanes to be dominant.

In people with node-negative disease, the results were found to be consistent across all comparisons with the addition of taxanes found to reduce costs and improve effectiveness. Therefore the addition of taxanes was found to be dominat in both the individual comparisons as well as the average result.

In people with triple-negative disease the addition of taxanes was found to be cost-effective in all modelled comparisons. In some cases, the addition of taxanes was found to increase costs and effectiveness with a resulting ICER value lower than the NICE threshold of £20,000 per QALY while in other cases it was found to be dominant. The average result showed the addition of taxanes to be dominant.

In people with HER2-positive disease, the results were found to be variable. In two of the comparisons (TAC versus FAC and doxorubicin/eprubicini+taxane versus doxorubicin/epirubicin+CMF) the addition of taxanes was found to be dominant. In the other three comparisons, the addition of taxanes was found to be more effective but also more costly. In two of these comparisons (EC+docetaxel versus FEC and AC/EC+taxane versus AC/EC) the addition of taxanes was not found to be cost-effective with an ICER value exceeding the NICE threshold of £20,000 per QALY. In the remaining comparison between FEC/FAC+taxane versus FEC/FAC, the addition of taxanes was found to be cost-effective with an ICER value below the NICE threshold of £20,000 per QALY. The average result showed the addition of taxanes to be more effective and less costly and therefore dominant.

In people with HER2-negative disease, the results were again found to be somewhat mixed. In most scenarios, the addition of taxanes was found to be more effective and also more costly. In one of these comparisons (TAC versus FAC) the addition of taxanes was found to be cost-effective with an ICER value below the NICE threshold of £20,000 per QALY. In two of these comparisons (EC+docetaxel versus FEC and AC/EC+taxane versus AC/EC) the addition of taxanes was not found to be cost-effective with an ICER values above the NICE threshold of £20,000 per QALY. In the comparison between FEC/FAC+taxane against FEC/FAC, the addition of taxanes was found to be less costly and less effective with an ICER value below the NICE threshold indicating that it is not cost-effective (not that the interpretation of the ICER value changes in this scenario) . The average result showed the addition of taxanes to be more costly and more effective but not cost-effective with an ICER above the NICE threshold of £20,000 per QALY.

In people with ER-positive disease, the addition of taxanes was found to be cost-effective in most cases. This includes scenarios where it was more effective and more costly with an

ICER below the NICE threshold as well as a scenario in which it was dominant. The comparison between AC/EC and AC/EC+taxane was the notable exception in which the addition of taxanes was found to be more costly and more effective but not cost-effective with an ICER well above the NICE threshold of £20,000 per QALY. The average result followed the pattern seen in most comparisons with the addition of taxanes shown to be more effective and more costly with an ICER below the NICE threshold..

In people with ER-negative disease, the addition of taxanes was found to be dominant in most comparisons. The exception was in the comparison between FEC/FAC and FEC/FAC+taxane where the addition of taxanes was found to be more costly and more effective but still cost-effective with an ICER below the NICE threshold of £20,000 per QALY. The average result followed the pattern seen in most comparisons with the addition of taxanes shown to be dominant.

In the overall 'mixed' population, the results were found to be variable. In two of the comparisons (FEC/FAC+taxane versus FEC/FAC and doxorubicin/epirubicin+taxane versus doxorubicin/epirubicin+CMF) the addition of taxanes was found to be dominant. In the remaining strategy (epirubicin+docetaxel versus epirubicin) the addition of taxanes was found to be more costly and more effective but not cost-effective with an ICER well above the NICE threshold of £20,000 per QALY. When taking the average of these divergent results, it was found that the addition of taxanes decreases costs and improves QALYs and was therefore dominant.

Table 39: Base case results for people with node-positive breast cancer

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
EC+docetaxel versus FEC					
FEC	£65,808	-	12.16	-	**-**
EC+docetaxel	£67,177	£1,368	12.38	*0.22*	**£6,284**
TAC versus FAC					
FAC	£51,665	-	10.40	-	**-**
TAC	£55,197	£3,532	11.09	*0.70*	**£5,081**
FEC/FAC+taxane versus FEC/FAC					
FEC/FAC	£46,725	-	8.94	-	**-**
FEC/FAC+taxane	£51,006	£4,281	9.33	*0.39*	**£10,874**
AC/EC+taxane versus AC/EC					
AC/EC	£344,783	-	12.10	-	**-**
AC/EC+taxane	£334,588	-£10,194	12.29	*0.19*	**Dominant**
Epirubicin+docetaxel versus epirubicin					
Epirubicin	£52,256	-	10.04	-	**-**
Epirubicin+docetaxel	£49,375	-£2,881	10.60	*0.57*	**Dominant**
Doxorubicin/epirubicin+taxane versus doxorubicin/epirubicin+CMF					
Doxorubicin/epirubicin+CMF	£75,075	-	7.04	-	**-**
Doxorubicin/epirubicin+taxane	£72,848	-£2,227	7.21	*0.17*	**Dominant**
Average					
Chemotherapy	£106,052	-	10.11	-	**-**
Chemotherapy+taxane	£105,032	-£1,020	10.48	*0.37*	**Dominant**

Table 40: Base case results for people with node-negative breast cancer

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
TAC versus FAC					
FAC	£58,800	-	14.48	-	**-**
TAC	£56,857	-£1,942	14.63	*0.15*	**Dominant**
FEC/FAC+taxane versus FEC/FAC					
FEC/FAC	£36,500	-	14.90	-	**-**
FEC/FAC+taxane	£35,454	-£1,046	14.99	*0.09*	**Dominant**
Average					
Chemotherapy	£47,650	-	14.69	-	**-**
Chemotherapy+taxane	£46,156	-£1,494	14.81	*0.12*	**Dominant**

Table 41: Base case results for people with triple-negative breast cancer

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
EC+docetaxel versus FEC					
FEC	£213,441	-	12.13	-	**-**
EC+docetaxel	£210,142	-£3,299	12.35	*0.22*	**Dominant**
TAC versus FAC					
FAC	£108,055	-	10.38	-	**-**
TAC	£110,720	£2,665	10.89	*0.50*	**£5,294**
FEC/FAC+taxane versus FEC/FAC					
FEC/FAC	£75,968	-	8.93	-	**-**
FEC/FAC+taxane	£74,675	-£1,293	9.16	*0.22*	**Dominant**
Doxorubicin/epirubicin+taxane versus doxorubicin/epirubicin+CMF					
Doxorubicin/epirubicin+CMF	£10,063	-	7.05	-	**-**
Doxorubicin/epirubicin+taxane	£10,885	£822	7.23	*0.17*	**£4,736**
Average					
Chemotherapy	£101,882	-	9.62	-	**-**
Chemotherapy+taxane	£101,605	-£276	9.90	*0.28*	**Dominant**

Table 42: Base case results for people with HER2-positive breast cancer

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
EC+docetaxel versus FEC					
FEC	£135,247	-	12.15	-	**-**
EC+docetaxel	£148,190	£12,943	12.36	*0.21*	**£60,249**
TAC versus FAC					
FAC	£154,258	-	10.37	-	**-**
TAC	£144,929	-£9,329	11.38	*1.01*	**Dominant**
FEC/FAC+taxane versus FEC/FAC					
FEC/FAC	£119,314	-	8.92	-	**-**
FEC/FAC+taxane	£132,413	£13,100	9.88	*0.96*	**£13,640**

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
AC/EC+taxane versus AC/EC					
AC/EC	£197,857	-	12.14	-	**-**
AC/EC+axane	£210,017	£12,159	12.32	*0.18*	**£67,495**
Doxorubicn/epirubicin+taxane versus doxorubicin/epirubicin+CMF					
Doxorubicin/epirubicin+CMF	£201,276	-	7.00	-	**-**
Doxorubicin/epirubicin+taxane	£156,573	-£44,703	7.19	*0.19*	**Dominant**
Average					
Chemotherapy	£161,590	-	10.12	-	**-**
Chemotherapy+taxane	£158,424	-£3,166	10.63	*0.51*	**Dominant**

1 **Table 43: Base case results for people with HER2-negative breast cancer**

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
EC+docetaxel versus FEC					
FEC	£88,553	-	12.16	-	**-**
EC+docetaxel	£94,899	£6,346	12.37	*0.22*	**£29,316**
TAC versus FAC					
FAC	£55,398	-	10.40	-	**-**
TAC	£61,362	£5,964	10.90	*0.50*	**£11,866**
FEC/FAC+taxane versus FEC/FAC					
FEC/FAC	£34,068	-	9.23	-	**-**
FEC/FAC+taxane	£28,946	-£5,122	8.67	*-0.56*	**£9,190**
AC/EC+taxane versus AC/EC					
AC/EC	£89,103	-	12.17	-	**-**
AC/EC+taxane	£107,046	£17,942	12.35	*0.18*	**£100,402**
Average					
Chemotherapy	£66,780	-	10.99	-	**-**
Chemotherapy+taxane	£73,063	£6,283	11.07	*0.09*	**£73,805**

2 **Table 44: Base case results for people with ER-positive breast cancer**

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
EC+docetaxel versus FEC					
FEC	£61,511	-	12.16	-	**-**
EC+docetaxel	£51,380	-£10,131	12.39	*0.22*	**Dominant**
FEC/FAC+taxane versus FEC/FAC					
FEC/FAC	£18,947	-	8.95	-	**-**
FEC/FAC+taxane	£20,973	£2,027	9.34	*0.39*	**£5,140**
AC/EC+taxane versus AC/EC					
AC/EC	£62,044	-	12.17	-	**-**
AC/EC+taxane	£69,723	£7,679	12.35	*0.18*	**£42,361**
Doxorubicin/epirubicin+taxane versus doxorubicin/epirubicin+CMF					

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Doxorubicin/epirubicin+CMF	£10,238	-	7.10	-	**-**
Doxorubicin/epirubicin+taxane	£10,852	£614	7.28	*0.17*	**£3,552**
Average					
Chemotherapy	£38,185	-	10.10	-	**-**
Chemotherapy+taxane	£38,232	£47	10.34	*0.24*	**£195**

Table 45: Base case results for people with ER-negative breast cancer

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
EC+docetaxel versus FEC					
FEC	£25,822	-	12.17	-	**-**
EC+docetaxel	£21,049	-£4,773	12.39	*0.22*	**Dominant**
FEC/FAC+taxane versus FEC/FAC					
FEC/FAC	£8,704	-	8.95	-	**-**
FEC/FAC+taxane	£14,561	£5,856	9.48	*0.53*	**£11,089**
AC/EC+taxane versus AC/EC					
AC/EC	£62,599	-	12.17	-	**-**
AC/EC+taxane	£58,147	-£4,451	12.36	*0.18*	**Dominant**
Average					
Chemotherapy	£32,375	-	11.10	-	**-**
Chemotherapy+taxane	£31,252	-£1,123	11.41	*0.31*	**Dominant**

Table 46: Overall 'mixed' population

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
FEC/FAC+taxane versus FEC/FAC					
FEC/FAC	£51,633	-	10.49	-	**-**
FEC/FAC+taxane	£45,035	-£6,598	10.64	*0.16*	**Dominant**
Epirubicin+docetaxel versus epirubicin					
Epirubicin	£143,677	-	14.33	-	**-**
Epirubicin+docetaxel	£147,745	£4,067	14.36	*0.03*	**£140,430**
Doxorubicin/epirubicin+taxane versus doxorubicin/epirubicin+CMF					
Doxorubicin/epirubicin+CMF	£71,646	-	11.13	-	**-**
Doxorubicin/epirubicin+taxane	£69,091	-£2,555	11.53	*0.39*	**Dominant**
Average					
Chemotherapy	£88,986	-	11.98	-	**-**
Chemotherapy+taxane	£87,290	-£1,695	12.18	*0.19*	**Dominant**

Deterministic sensitivity analysis results

A series of deterministic sensitivity analyses was conducted, whereby one input parameter was changed, the model was re-run and the new cost-effectiveness result was recorded.

This form of analysis is a useful way of estimating uncertainty and determining the key drivers of the model results.

The results of the deterministic sensitivity analysis are presented in Table 47 showing the ICER result for a comparison between chemotherapy and taxanes versus chemotherapy alone. For simplicity, the results are presented for the average result across all comparisons in each of the subgroups.

The results of the analysis are highly sensitive to changes in the HRs for OS and DFS. Indeed, chemotherapy alone is preferred in all comparisons when the upper HR values for OS and DFS are applied. On the other hand, chemotherapy and taxanes are preferred in all comparisons when the lower HR values for OS and DFS are applied.

A further sensitivity analysis considered only those comparisons in which consistent chemotherapy regimens were used in both the chemotherapy and chemotherapy and taxanes arms. This removes the potential for differences other than those related to the taxane to influence the results. It can be seen that the results in this scenario do not differ substantially from the base case results with the addition of taxanes to chemotherapy found to be cost-effective in all subgroups except people with HER2 negative breast cancer.

Table 47: Deterministic sensitivity analysis results

Change made	Node-positive	Node-negative	Triple-negative	HER2-positive	HER2-negative	ER-positive	ER-negative	Overall
Base case	**Dominant**	**Dominant**	**Dominant**	**Dominant**	**£73,805**	**£195**	**Dominant**	**Dominant**
Upper HR for mortality	Dominant	£33,303*	£31,749*	£1,017,300	£4,591*	£36,266*	£38,004	£204,952*
Lower HR for mortality	£7,679	Dominant	£12,823	£6,684	£26,901	£6,417	£4,770	£3,573
Upper HR for recurrence	£15,368	£16,065	£97,000	£89,538	£281,923	£49,558	£22,656	£27,840
Lower HR for recurrence	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
Upper HR for mortality and recurrence	Dominant	£8,810*	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Lower HR for mortality and recurrence	Dominant	Dominant	Dominant	Dominant	£3,789	Dominant	Dominant	Dominant

Change made	Node-positive	Node-negative	Triple-negative	HER2-positive	HER2-negative	ER-positive	ER-negative	Overall
Baseline OS = 80%	Dominant	Dominant	Dominant	Dominant	£60,419	£9,950	£2,503	Dominant
Baseline OS = 70%	£2,964	Dominant	£3,504	Dominant	£62,678	£14,180	£6,693	£6,415
Baseline DFS = 80%	£2,223	Dominant	£4,174	£12,507	£73,024	£3,830	£2,074	Dominant
Baseline DFS = 70%	Dominant	Dominant	£2,610	£5,636	£82,533	£948	Dominant	Dominant6
Treatment effect duration = 10 years	Dominant	Dominant	Dominant	Dominant	£124,093	Dominant	Dominant	Dominant
Treatment effect duration = 20 years	Dominant	Dominant	Dominant	Dominant	£99,851	Dominant	Dominant	Dominant
Lifetime treatment effect duration	Dominant	Dominant	Dominant	Dominant	£94,164	Dominant	Dominant	Dominant
Reduced G-CSF cost	Dominant	Dominant	Dominant	Dominant	£71,105	Dominant	Dominant	Dominant
Consistent regimens only	Dominant	Dominant	Dominant	Dominant	Dominated	£13,788	£1,972	£664

** ICER results show a scenario where the addition of taxanes was found to be less effective and less expensive. Therefore, interpretation of the ICER result changes with values above £20,000 per QALY indicating cost-effectiveness.*

Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base-case were replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using cost-effectiveness acceptability curves (CEAC). The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

The results of the probabilistic sensitivity analysis are presented in the CEACs below (Figure 134: Cost-effectiveness acceptability curve for people with node positive breast cancer for each of the subgroups. For simplicity, the results are presented for the average result across all treatment comparisons in each of the subgroups.

In all the subgroups it can be seen that, as the threshold increases, the probability of chemotherapy being cost-effective decreases while the probability of chemotherapy and taxane being cost-effective increases. However, while the pattern is very similar in all comparisons the probability of chemotherapy and taxanes being cost-effective at the threshold of £20,000 per QALY used by NICE varies significantly. In the node-positive, node-negative, triple-negative, HER2-positive, ER-positive, ER-negative subgroups and the overall population it can be seen that chemotherapy and taxanes have the highest probability of being cost-effective at a threshold of £20,000 per QALY (probabilities of 100%, 98%, 77%, 88%, 90%, 99% and 99%, respectively). In the HER2-negative population, chemotherapy alone had the highest probability of being cost-effective at a threshold of £20,000 per QALY (86%).

Figure 134: Cost-effectiveness acceptability curve for people with node positive breast cancer

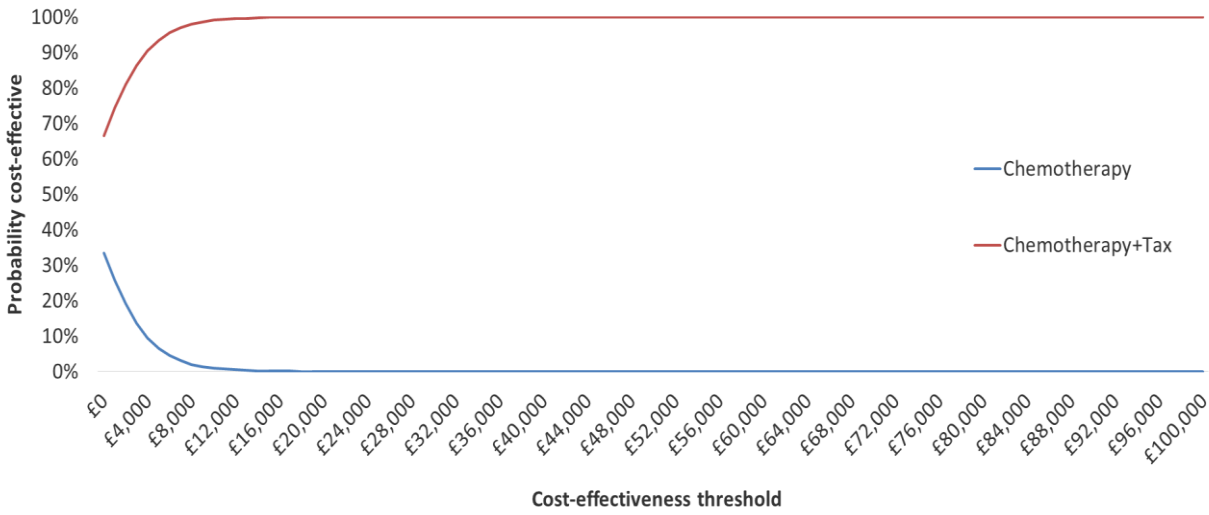


Figure 135: Cost-effectiveness acceptability curve for people with node negative breast cancer

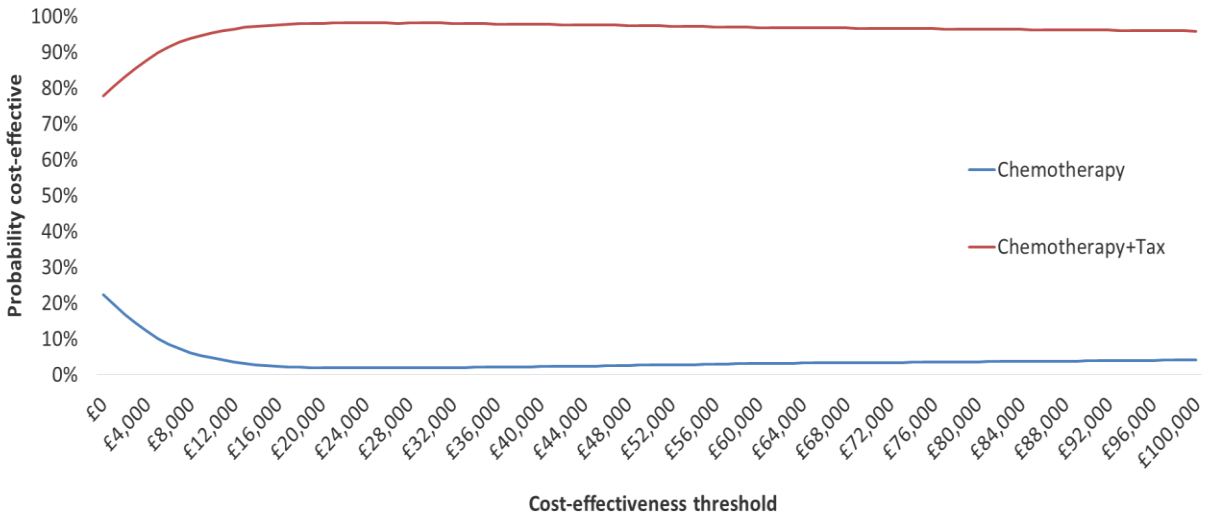


Figure 136: Cost-effectiveness acceptability curve for people with triple negative breast cancer

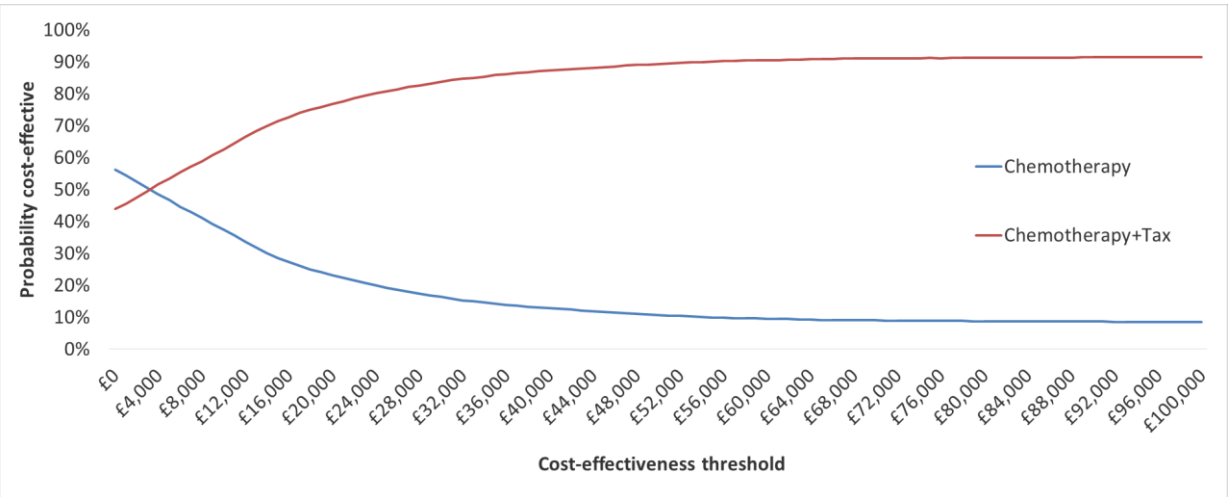


Figure 137: Cost-effectiveness acceptability curve for people with HER2-positive breast cancer

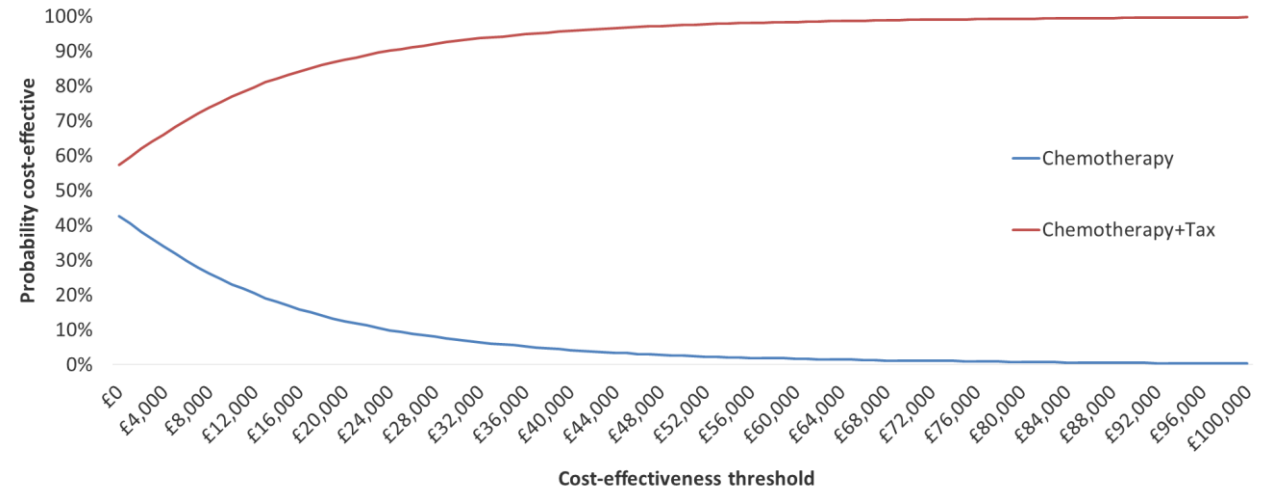


Figure 138: Cost-effectiveness acceptability curve for people with HER2-negative breast cancer

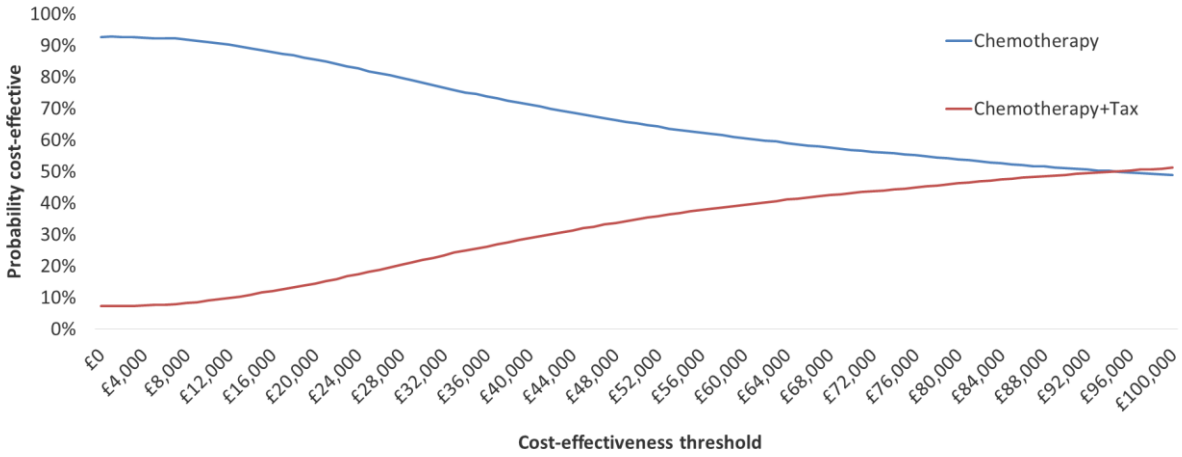


Figure 139: Cost-effectiveness acceptability curve for people with ER-positive breast cancer

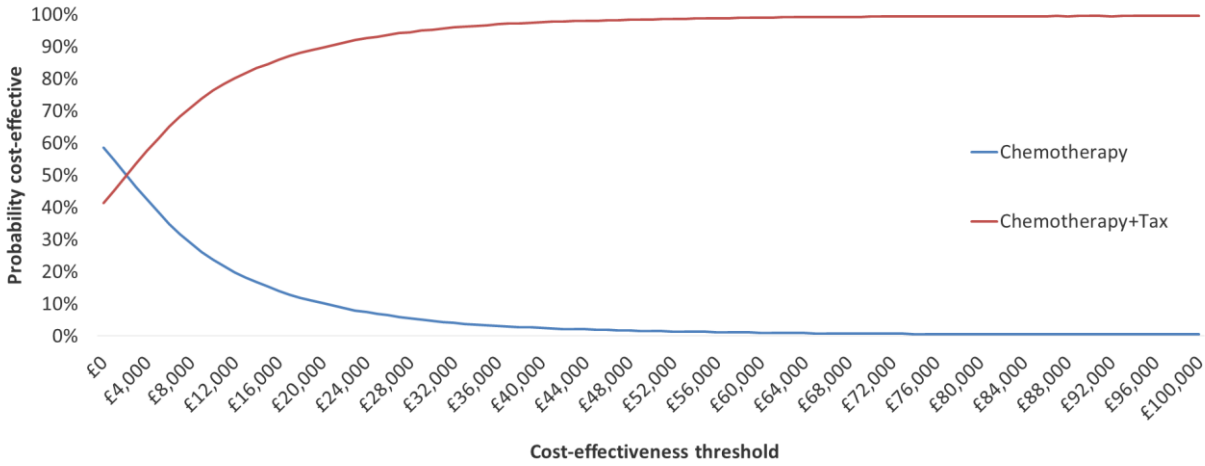


Figure 140: Cost-effectiveness acceptability curve for people with ER-negative breast cancer

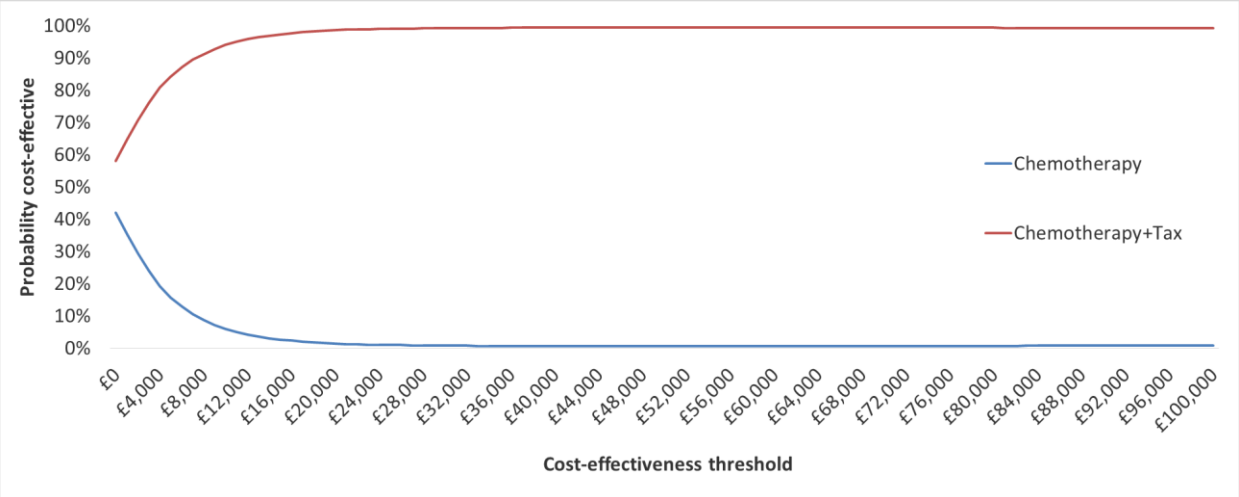
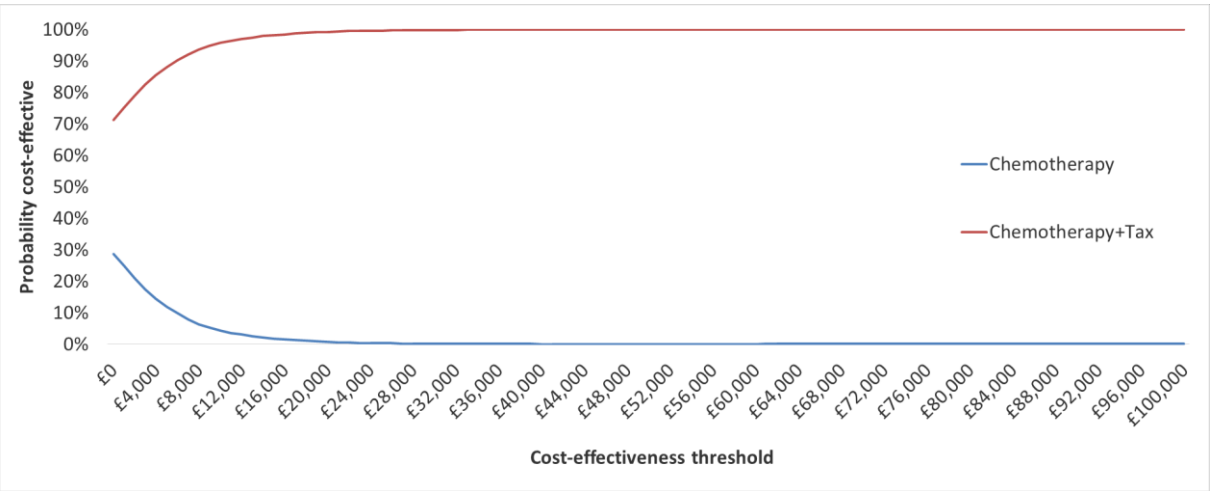


Figure 141: Cost-effectiveness acceptability curve for overall 'mixed' population



Probabilistic base case results

In addition to the deterministic results, the base case results were also generated probabilistically. In this analysis the mean total costs and QALYs were recorded after 10,000 probabilistic runs of the analysis. The probabilistic base case results are presented Table 48. It can be seen that the results do not differ substantially from the deterministic base case with the conclusions of the analysis unchanged.

Table 48: Probabilistic base case results

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Node-positive					
Chemotherapy	£106,871	-	10.13	-	-
Chemotherapy+taxane	£105,726	-£1,145	10.49	*0.36*	**Dominant**
Node-negative					

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Chemotherapy	£48,122	-	14.68	-	**-**
Chemotherapy+taxane	£46,577	-£1,545	14.79	*0.11*	**Dominant**
Triple-negative					
Chemotherapy	£102,886	-	9.64	-	**-**
Chemotherapy+taxane	£104,129	£1,243	9.89	*0.25*	**£4,968**
HER2-positive					
Chemotherapy	£161,035	-	10.13	-	**-**
Chemotherapy+taxane	£159,563	-£1,472	10.62	*0.49*	**Dominant**
HER2-negative					
Chemotherapy	£67,055	-	11.00	-	**-**
Chemotherapy+taxane	£73,842	£6,788	11.06	*0.07*	**£98,857**
ER-positive					
Chemotherapy	£38,546	-	10.11	-	**-**
Chemotherapy+taxane	£39,274	£728	10.34	*0.23*	**£3,163**
ER-negative					
Chemotherapy	£32,612	-	11.10	-	**-**
Chemotherapy+taxane	£32,078	-£534	11.40	*0.29*	**Dominant**
Overall					
Chemotherapy	£82,094	-	11.63	-	**-**
Chemotherapy+taxane	£80,568	-£1,526	11.82	*0.19*	**Dominant**

Conclusion

It is difficult to draw any firm conclusion around cost-effectiveness in this area as the clinical evidence upon which it is based is too uncertain. In particular, there is a lack of high quality clinical evidence showing clear differences between the approaches. However, it does appear that in most scenarios where taxanes were assumed to improve overall and disease-free survival, their use would be cost-effective. Furthermore, the evidence is somewhat variable for the different subgroups with a greater degree of certainty around some of the higher risk subgroups such as people with node-positive disease.

Appendix K – Excluded studies

Clinical studies

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
Abe, H., Mori, T., Kawai, Y., Cho, H., Kubota, Y., Umeda, T., Kurumi, Y., Tani, T., Feasibility and toxicity of docetaxel before or after fluorouracil, epirubicin and cyclophosphamide as adjuvant chemotherapy for early breast cancer, International Journal of Clinical Oncology, 18, 487-491, 2013	Comparison between different taxane regimens
Andergassen, U, Kasprowicz, Ns, Hepp, P, Schindlbeck, C, Harbeck, N, Kiechle, M, Sommer, H, Beckmann, Mw, Friese, K, Janni, W, Rack, B, Scholz, C, Participation in the success-A Trial improves intensity and quality of care for patients with primary breast cancer, Geburtshilfe und Frauenheilkunde, 73, 63-9, 2013	Outcome outside scope: satisfaction in participating trial centres
Andre,F., Broglio,K., Roche,H., Martin,M., Mackey,J.R., Penault-Llorca,F., Hortobagyi,G.N., Pusztai,L., Estrogen receptor expression and efficacy of docetaxel-containing adjuvant chemotherapy in patients with node-positive breast cancer: results from a pooled analysis, Journal of Clinical Oncology, 26, 2636-2643, 2008	Reports same outcomes and population as Coudert 2012 and Mackey 2013 over shorter follow-up period
Anonymous,, NSABP B-38: Definitive analysis of a randomized adjuvant trial comparing dose-dense (DD) AC->Paclitaxel (P) plus gemcitabine (G) with DD AC->P and with docetaxel, doxorubicin, and cyclophosphamide (TAC) in women with operable, node-positive breast cancer, Clinical Advances in Hematology and Oncology, 10, 11-13, 2012	Abstract only
Au, H. J., Eiermann, W., Robert, N. J., Pienkowski, T., Crown, J., Martin, M., Pawlicki, M., Chan, A., Mackey, J., Glaspy, J., Pinter, T., Liu, M. C., Fornander, T., Sehdev, S., Ferrero, J. M., Bee, V., Santana, M. J., Miller, D. P., Lalla, D., Slamon, D. J., Health-related quality of life with adjuvant docetaxel- and trastuzumab-based regimens in patients with node-positive and high-risk node-negative, her2-positive early breast cancer: Results from the BCIRG 006 study, Oncologist, 18, 812-818, 2013	Insufficient presentation of results
Au, H-J, Robert, N, Eiermann, W, Pienkowski, T, Crown, J, Martin, M, BCIRG 006: quality of life (QoL) of patients (pts) treated with docetaxel and trastuzumab-based regimens in node positive and high risk node negative HER2 positive early breast cancer, 2007	Abstract only
Berger, A. M., Lockhart, K., Agrawal, S., Variability of patterns of fatigue and quality of life over time based on different breast cancer adjuvant chemotherapy regimens, Oncology nursing forum, 36, 563-70, 2009	Non-RCT
Bianco, Ar, Matteis, A, Manzione, L, Boni, C, Sequential epirubicin-docetaxel-CMF as adjuvant therapy of early breast cancer: Results of the Taxit216 multicenter phase III trial, Journal of Clinical Oncology, 24, 8s, 2006	Abstract only

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
Bines, J., Earl, H., Buzaid, A. C., Saad, E. D., Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: Does the sequence matter?, Annals of Oncology, 25, 1079-1085, 2014	Includes non-RCTs
Boccardo,F., Amadori,D., Guglielmini,P., Sismondi,P., Farris,A., Agostara,B., Gambi,A., Catalano,G., Faedi,M., Rubagotti,A., Epirubicin followed by cyclophosphamide, methotrexate and 5-fluorouracil versus paclitaxel followed by epirubicin and vinorelbine in patients with high-risk operable breast cancer, Oncology, 78, 274-281, 2010	Contains vinorelbine – not routinely used in UK
Bono, P., Kellokumpu-Lehtinen, P. L., Alanko, T., Kokko, R., Asola, R., Turpeenniemi-Hujanen, T., Jyrkkio, S., Kataja, V., Leinonen, M., Joensuu, H., Docetaxel 100 versus 80 mg/m² as adjuvant treatments of early breast cancer: An exploratory analysis of a randomised trial, Annals of Oncology, 20, 595-596, 2009	Non-RCT
Brain, E., Levy, C., Serin, D., Roche, H., Spielmann, M., Delva, R., Veyret, C., Mauriac, L., Rios, M., Martin, A. L., Jimenez, M., Asselain, B., Gauthier, M., Bonnetain, F., Fumoleau, P., High rate of extra-haematological toxicity compromises dose-dense sequential adjuvant chemotherapy for breast cancer, British journal of cancer, 105, 1480-6, 2011	Compares different taxane regimens
Brandberg, Y., Johansson, H., Hellstrom, M., Foukakis, T., Gnant, M., Von Minckwitz, G., Bergh, J. C. S., The adjuvant panther study: A randomized comparison between dosedense and tailored epirubicin (E), cyclophosphamide (C) and docetaxel (D) vs. standard dose 5-fluorouracil (F), epirubicin (E), cyclophosphamide (C) and docetaxel-Health-related quality of life during ongoing therapy, Journal of Clinical Oncology. Conference, 34, 2016	Abstract only
Bria, E., Nistico, C., Cuppone, F., Carlini, P., Ciccarese, M., Milella, M., Natoli, G., Terzoli, E., Cognetti, F., Giannarelli, D., Benefit of taxanes as adjuvant chemotherapy for early breast cancer: Pooled analysis of 15,500 patients, Cancer, 106, 2337-2344, 2006	Intevention outside scope of protocol - Includes neoadjuvant chemotherapy
Budd, G. T., Barlow, W. E., Moore, H. C. F., Hobday, T. J., Stewart, J. A., Isaacs, C., Salim, M., Cho, J. K., Rinn, K. J., Albain, K. S., Chew, H. K., Burton, G. V., Moore, T. D., Srkalovic, G., McGregor, B. A., Flaherty, L. E., Livingston, R. B., Lew, D. L., Gralow, J. R., Hortobagyi, G. N., SWOG S0221: A phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer, Journal of Clinical Oncology, 33, 58-64, 2015	Comparison between different taxane regimens
Burdette-Radoux, S., Wood, M. E., Olin, J. J., Laughlin, R. S., Crocker, A. M., Ashikaga, T., Muss, H. B., Phase I/II trial of adjuvant dose-dense docetaxel/epirubicin/cyclophosphamide (TEC) in stage II and III breast cancer, Breast Journal, 13, 274-80, 2007	Non-RCT
Burnell, M., Levine, M. N., Chapman, J. A. W., Bramwell, V., Gelmon, K., Walley, B., Vandenberg, T., Chalchal, H., Albain, K. S., Perez, E. A., Rugo, H., Pritchard, K., O'Brien, P., Shepherd, L. E., Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer, Journal of Clinical Oncology, 28, 77-82, 2010	Contains ciprofloxacin – not routinely used in UK

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
Coudert, B, Campone, M, Spielmann, M, Symann, M, Eichler, F, Serin, D, Benefit of the Sequential Administration of Docetaxel after Standard FEC Regimen for Node-Positive Breast Cancer: Long-Term Follow-Up Results of the FNCLCC-PACS 01 Trial, 69, 2010	Conference presentation
Dang, C., Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by paclitaxel for early breast cancer, Current Breast Cancer Reports, 1, 1-2, 2009	Commentary
De Laurentiis, M., Cancello, G., D'Agostino, D., Giuliano, M., Giordano, A., Montagna, E., Lauria, R., Forestieri, V., Esposito, A., Silvestro, L., Pennacchio, R., Criscitiello, C., Montanino, A., Limite, G., Bianco, A. R., De Placido, S., Taxane-based combinations as adjuvant chemotherapy of early breast cancer: A meta-analysis of randomized trials, Journal of Clinical Oncology, 26, 44-53, 2008	Intevention outside scope of protocol - Includes neoadjuvant chemotherapy
Del Mastro, L., Costantini, M., Durando, A., Michelotti, A., Danese, S., Aitini, E., Olmeo, N., Pronzato, P., Venturini, M., Gruppo Oncologico Nord Ovest - Mammella, Intergruppo, Cyclophosphamide, epirubicin, and 5-fluorouracil versus epirubicin plus paclitaxel in node-positive early breast cancer patients: A randomized, phase III study of Gruppo Oncologico Nord Ovest-Mammella Intergruppo Group, Journal of Clinical Oncology, 26, 516, 2008	Abstract only
Eckhoff, L., Knoop, A. S., Jensen, M. B., Ejlertsen, B., Ewertz, M., Risk of docetaxel-induced peripheral neuropathy among 1,725 Danish patients with early stage breast cancer, Breast Cancer Research and Treatment, 142, 109-118, 2013	No anthracycline in experimental arm
Eiermann,W., Pienkowski,T., Crown,J., Sadeghi,S., Martin,M., Chan,A., Saleh,M., Sehdev,S., Provencher,L., Semiglazov,V., Press,M., Sauter,G., Lindsay,M.A., Riva,A., Buyse,M., Drevot,P., Taupin,H., Mackey,J.R., Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG-005 trial, Journal of Clinical Oncology, 29, 3877-3884, 2011	Includes same outcomes and populations as Mackey 2016 with shorter follow-up periods
Ellis, Pa, Barrett-Lee, Pj, Bloomfield, D, Cameron, Da, Hall, E, JohnsonL,, Preliminary results of the UK Taxotere as Adjuvant Chemotherapy (TACT) Trial, 2007	Abstract only
Ferguson, Thomas, Wilcken, Nicholas, Vagg, Rosemary, Ghersi, Davina, Nowak, Anna K, Taxanes for adjuvant treatment of early breast cancer, Cochrane Database of Systematic Reviews, 2007	Intevention outside scope of protocol - Includes neoadjuvant chemotherapy
Fernandes, R., Mazzarello, S., Hutton, B., Shorr, R., Majeed, H., Ibrahim, M. F. K., Jacobs, C., Ong, M., Clemons, M., Taxane acute pain syndrome (TAPS) in patients receiving taxane-based chemotherapy for breast cancer-a systematic review, Supportive Care in Cancer, 24, 3633-3650, 2016	Includes non-anthracycline regimens
Fountzilas, G, Papadimitriou, C, Dafni, U, Bafaloukos, D, Skarlos, D, Moulopoulos, La, Razis, E, Kalofonos, Hp, Aravantinos, G, Briassoulis, E, Papakostas, P, Abela, K, Gogas, E, Kosmidis, P, Pavlidis, N, Dimopoulos, Ma, Dose-dense sequential chemotherapy with epirubicin and paclitaxel versus the combination, as first-line	Includes same outcomes and population as Fountzilas 2014 with shorter follow-up

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
chemotherapy, in advanced breast cancer: a randomized study conducted by the Hellenic Cooperative Oncology Group, Journal of Clinical Oncology, 19, 2232-2239, 2012	
Fountzilas, G., Dafni, U., Gogas, H., Linardou, H., Kalofonos, H. P., Briasoulis, E., Pectasides, D., Samantas, E., Bafaloukos, D., Stathopoulos, G. P., Karina, M., Papadimitriou, C., Skarlos, D., Pisanidis, N., Papakostas, P., Markopoulos, C., Tzorakoeleftherakis, E., Dimitrakakis, K., Makrantonakis, P., Xiros, N., Polichronis, A., Varthalitis, I., Karanikiotis, C., Dimopoulos, A. M., Postoperative dose-dense sequential chemotherapy with epirubicin, paclitaxel and CMF in patients with high-risk breast cancer: Safety analysis of the Hellenic Cooperative Oncology Group randomized phase III trial HE 10/00, Annals of Oncology, 19, 853-860, 2008	Includes same outcomes and population as Fountzilas 2014 and Gogas 2012 with shorter follow-up period
Fountzilas, G., Dafni, U., Papadimitriou, C., Timotheadou, E., Gogas, H., Eleftheraki, A. G., Xanthakis, I., Christodoulou, C., Koutras, A., Papandreou, C. N., Papakostas, P., Miliaras, S., Markopoulos, C., Dimitrakakis, C., Korantzopoulos, P., Karanikiotis, C., Bafaloukos, D., Kosmidis, P., Samantas, E., Varthalitis, I., Pavlidis, N., Pectasides, D., Dimopoulos, M. A., Dose-dense sequential adjuvant chemotherapy followed, as indicated, by trastuzumab for one year in patients with early breast cancer: First report at 5-year median follow-up of a Hellenic Cooperative Oncology Group randomized phase III trial, BMC cancer, 14 (1) (no pagination), 2014	Compares different taxane regimens
Frasci, G, D'Aiuto, G, Comella, P, Thomas, R, Botti, G, Bonito, M, Rosa, V, Iodice, G, Rubulotta, Mr, Comella, G, Weekly cisplatin, epirubicin, and paclitaxel with granulocyte colony-stimulating factor support vs triweekly epirubicin and paclitaxel in locally advanced breast cancer: final analysis of a sicog phase III study, British Journal of Cancer, 95, 1005-12, 2006	Intevention outside scope of protocol - Neoadjuvant chemotherapy
Gines, J., Sabater, E., Martorell, C., Grau, M., Monroy, M., Casado, M. A., Efficacy of taxanes as adjuvant treatment of breast cancer: A review and meta-analysis of randomised clinical trials, Clinical and Translational Oncology, 13, 485-498, 2011	Insufficient information about included studies
Gogas, H., Dafni, U., Karina, M., Papadimitriou, C., Batistatou, A., Bobos, M., Kalofonos, H. P., Eleftheraki, A. G., Timotheadou, E., Bafaloukos, D., Christodoulou, C., Markopoulos, C., Briasoulis, E., Papakostas, P., Samantas, E., Kosmidis, P., Stathopoulos, G. P., Karanikiotis, C., Pectasides, D., Dimopoulos, M. A., Fountzilas, G., Postoperative dose-dense sequential versus concomitant administration of epirubicin and paclitaxel in patients with node-positive breast cancer: 5-year results of the Hellenic Cooperative Oncology Group HE 10/00 phase III Trial, Breast Cancer Research & Treatment, 132, 609-19, 2012	Compares different taxane regimens
Goldstein, L. J., O'Neill, A., Sparano, J. A., Perez, E. A., Shulman, L. N., Martino, S., Davidson, N. E., Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American Breast Cancer Intergroup Trial E 2197, Journal of clinical oncology, 26, 4092-9, 2008	Contains ciprofloxacin – not routinely used in UK
Hall, E., Cameron, D., Waters, R., Barrett-Lee, P., Ellis, P., Russell, S., Bliss, J. M., Hopwood, P., Comparison of patient reported quality of life and impact of treatment side effects experienced with a taxane-containing	Insufficient presentation of HRQoL results - other outcomes reported in Ellis 2009

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
regimen and standard anthracycline based chemotherapy for early breast cancer: 6 year results from the UK TACT trial (CRUK/01/001), European Journal of Cancer, 50, 2375-2389, 2014	
Han,H.S., Ro,J., Lee,K.S., Nam,B.H., Seo,J.A., Lee,D.H., Lee,H., Lee,E.S., Kang,H.S., Kim,S.W., Analysis of chemotherapy-induced amenorrhea rates by three different anthracycline and taxane containing regimens for early breast cancer, Breast Cancer Research and Treatment, 115, 335-342, 2009	Intevention outside scope of protocol - Neoadjuvant chemotherapy
Hatam, N., Ahmadloo, N., Ahmad Kia Daliri, A., Bastani, P., Askarian, M., Quality of life and toxicity in breast cancer patients using adjuvant TAC (docetaxel, doxorubicin, cyclophosphamide), in comparison with FAC (doxorubicin, cyclophosphamide, 5-fluorouracil), Archives of Gynecology and Obstetrics, 284, 215-220, 2011	Non-randomised study
Helen, G., Pentheroudakis, G., Antoniadis, A., Murray, S., Fountzilas, G., The role of taxanes in the management of patients with early breast cancer: A review of the clinical evidence and molecular mechanisms of resistance, Cancer and Chemotherapy Reviews, 3, 65-76, 2008	Insufficient information about included studies
Hopwood, P., Ridolfi, A., Russell, S., Peckitt, C., Bliss, J. M., Hall, E., Johnson, L., Barrett-Lee, P., Ellis, P., Cameron, D. A., Tact Trial Management Group, Impact on quality of life (QoL) of FEC-T compared with FEC or E-CMF: UK Taxotere as Adjuvant Chemotherapy Trial (TACT) 2-year follow-up, Journal of Clinical Oncology, 26, 548, 2008	Abstract only
Hugenholtz-Wamsteker, W., Robbeson, C., Nijs, J., Hoelen, W., Meeus, M., The effect of docetaxel on developing oedema in patients with breast cancer: a systematic review, European Journal of Cancer Care, 25, 269-79, 2016	Includes non-anthracycline regimens
Hugh, J., Hanson, J., Cheang, M. C. U., Nielsen, T. O., Perou, C. M., Dumontet, C., Reed, J., Krajewska, M., Treilleux, I., Rupin, M., Magherini, E., Mackey, J., Martin, M., Vogel, C., Breast cancer subtypes and response to docetaxel in node-positive breast cancer: Use of an immunohistochemical definition in the BCIRG 001 trial, Journal of Clinical Oncology, 27, 1168-1176, 2009	Reports same outcomes and population as Mackey 2013 over shorter follow-up periods
Jacquin, J. P., Jones, S., Magne, N., Chapelle, C., Ellis, P., Janni, W., Mavroudis, D., Martin, M., Laporte, S., Docetaxel-containing adjuvant chemotherapy in patients with early stage breast cancer. Consistency of effect independent of nodal and biomarker status: A meta-analysis of 14 randomized clinical trials, Breast Cancer Research and Treatment, 134, 903-913, 2012	Insufficient information about included studies
Janni, W, Harbeck, N, Sommer, H, Rack, B, Augustin, D, Simon, W, Final toxicity analysis of the ADEBAR phase III study evaluating the role of docetaxel in the adjuvant therapy of breast cancer patients with extensive lymph node involvement, 2007	Abstract only
Janni, W, Harbeck, N, Sommer, H, Rack, B, Augustin, D, Simon, W, Sequential Treatment with Epirubicin/Cyclophosphamide, Followed by Docetaxel Is Equieffective, but Less Toxic Than FEC120 in the Adjuvant Treatment of Breast Cancer Patients with Extensive Lymph Node Involvement: The German	Conference presentation

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
ADEBAR Phase III Study, Thirty-second Annual CTRC-AACR San Antonio Breast Cancer Symposium, 69, 2009	
Janni, W. J., Genss, E., Sommer, H. L., Rack, B. K., Schneeweibeta, A., Rezai, M., Hilfrich, J., Schneider, A., Lichtenegger, W., Beckmann, M. W., The SUCCESS-Trial: Toxicity analysis of a phase III study evaluating the role of docetaxel and gemcitabine in the adjuvant therapy of breast cancer patients, Journal of Clinical Oncology, 26, 551, 2008	Abstract only
Kantelhardt, E. J., Vetter, M., Schmidt, M., Veyret, C., Augustin, D., Hanf, V., Meisner, C., Paepke, D., Schmitt, M., Sweep, F., von Minckwitz, G., Martin, P. M., Jaenicke, F., Thomssen, C., Harbeck, N., Prospective evaluation of prognostic factors uPA/PAI-1 in node-negative breast cancer: phase III NNBC3-Europe trial (AGO, GBG, EORTC-PBG) comparing 6xFEC versus 3xFEC/3xDocetaxel, BMC cancer, 11, 140, 2011	Protocol only
Leinert, E., Singer, S., Janni, W., Harbeck, N., Weissenbacher, T., Rack, B., Augustin, D., Wischnik, A., Kiechle, M., Ettl, J., Fink, V., Schwentner, L., Eichler, M., The Impact of Age on Quality of Life in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Comparative Analysis From the Prospective Multicenter Randomized ADEBAR trial, Clinical Breast Cancer., 10, 2016	Additional subgroup analysis for ADEBAR trial not of interest in guideline review
Loesch,D., Greco,F.A., Senzer,N.N., Burris,H.A., Hainsworth,J.D., Jones,S., Vukelja,S.J., Sandbach,J., Holmes,F., Sedlacek,S., Pippen,J., Lindquist,D., McIntyre,K., Blum,J.L., Modiano,M.R., Boehm,K.A., Zhan,F., Asmar,L., Robert,N., Phase III multicenter trial of doxorubicin plus cyclophosphamide followed by paclitaxel compared with doxorubicin plus paclitaxel followed by weekly paclitaxel as adjuvant therapy for women with high-risk breast cancer, Journal of Clinical Oncology, 28, 2958-2965, 2010	Comparison between different taxane regimens
Loi, S., Sirtaine, N., Piette, F., Salgado, R., Viale, G., Van Eenoo, F., Rouas, G., Francis, P., Crown, J. P. A., Hitre, E., De Azambuja, E., Quinaux, E., Di Leo, A., Michiels, S., Piccart, M. J., Sotiriou, C., Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98, Journal of Clinical Oncology, 31, 860-867, 2013	Comparison of lymphocyte-predominant breast cancer
Loibl, S., von Minckwitz, G., Harbeck, N., Janni, W., Elling, D., Kaufmann, M., Eggemann, H., Nekljudova, V., Sommer, H., Kiechle, M., Kummel, S., Clinical feasibility of (neo)adjuvant taxane-based chemotherapy in older patients: analysis of >4,500 patients from four German randomized breast cancer trials, Breast Cancer Research, 10, R77, 2008	Intevention outside scope of protocol - Includes neoadjuvant chemotherapy
Lopez, M, Brandi, M, Foggi, P, Giotta, F, Toxicity of epirubicin and cyclophosphamide (EC) vs. docetaxel (D) followed by EC in the adjuvant (adj) treatment of node positive breast cancer. A multicenter randomized phase III study (GOIM9902), Journal of Clinical Oncology, 24, 570s, 2006	Abstract only
Mackey, J. R., Pienkowski, T., Crown, J., Sadeghi, S., Martin, M., Chan, A., Saleh, M., Sehdev, S., Provencher, L., Semiglazov, V., Press, M. F., Sauter, G., Lindsay, M., Houe, V., Buyse, M., Drevot, P., Hitier,	Compares different taxane regimens

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
S., Bensfia, S., Eiermann, W., Long-term outcomes after adjuvant treatment of sequential versus combination docetaxel with doxorubicin and cyclophosphamide in node-positive breast cancer: BCIRG-005 randomized trial, Annals of oncology, 27, 1041-1047, 2016	
Mansi, J. L., Yellowlees, A., Lipscombe, J., Earl, H. M., Cameron, D. A., Coleman, R. E., Perren, T., Gallagher, C. J., Quigley, M., Crown, J., Jones, A. L., Highley, M., Leonard, R. C. F., Jeffry Evans, T. R., Five-year outcome for women randomised in a phase III trial comparing doxorubicin and cyclophosphamide with doxorubicin and docetaxel as primary medical therapy in early breast cancer: An Anglo-Celtic Cooperative Oncology Group Study, Breast Cancer Research and Treatment, 122, 787-794, 2010	Intevention outside scope of protocol - Neoadjuvant chemotherapy
Margolin, S., Bengtsson, N. O., Carlsson, L., Edlund, P., Hellstrom, M., Karlsson, P., Lidbrink, E., Linderholm, B., Lindman, H., Malmstrom, P., Pettersson Skolld, D., Soderberg, M., Villman, K., Bergh, J., A randomised feasibility/phase II study (SBG 2004-1) with dose-dense/tailored epirubicin, cyclophoshamide (EC) followed by docetaxel (T) or fixed dosed dose-dense EC/T versus T, doxorubicin and C (TAC) in node-positive breast cancer, Acta Oncologica, 50, 35-41, 2011	Comparison between different taxane regimens
Martin, M., Lluch, A., Segu i, M. A., Ruiz, A., Ramos, M., Adrover, E., Rodriguez-Lescure, A., Grosse, R., Calvo, L., Anton, A., TAC versus FAC as adjuvant chemotherapy for high-risk node-negative breast cancer: Results of the geicam 9805 trial, Annals of Oncology, 19, viii77, 2008	Conference presentation
Martin, M., Lluch, A., Segui, M. A., Ruiz, A., Ramos, M., Adrover, E., Rodriguez-Lescure, A., Grosse, R., Calvo, L., Fernandez-Chacon, C., Roset, M., Anton, A., Isla, D., del Prado, P. M., Iglesias, L., Zaluski, J., Arcusa, A., Lopez-Vega, J. M., Munoz, M., Mel, J. R., Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC): Impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen, Annals of Oncology, 17, 1205-1212, 2006	Insufficient presentation of results
Martin, M., Simon, A. R., Borrego, M. R., Ribelles, N., Rodriguez-Lescure, A., Munoz-Mateu, M., Gonzalez, S., Vila, M. M., Barnadas, A., Ramos, M., Del Barco Berron, S., Jara, C., Calvo, L., Martinez-Janez, N., Fernandez, C. M., Rodriguez, C. A., De Duenas, E. M., Andres, R., Plazaola, A., De La Haba-Rodriguez, J., Lopez-Vega, J. M., Adrover, E., Ballesteros, A. I., Santaballa, A., Sanchez-Rovira, P., Baena-Canada, J. M., Casas, M., Del Carmen Camara, M., Carrasco, E. M., Lluch, A., Epirubicin plus cyclophosphamide followed by docetaxel versus epirubicin plus docetaxel followed by capecitabine as adjuvant therapy for node-positive early breast cancer: Results from the GEICAM/2003-10 study, Journal of Clinical Oncology, 33, 3788-3795, 2015	Contains capecitabine – not routinely used in UK
Mavroudis, D., Malamos, N., Papakotoulas, P., Adamou, A., Christophyllakis, C., Ziras, N., Syrigos, K., Kakolyris, S., Kouroussis, C., Georgoulias, V., Randomized phase III trial comparing the sequential administration of docetaxel followed by epirubicin plus cyclophosphamide versus FE₇₅C as	Abstract only

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
adjuvant chemotherapy in axillary lymph node-positive breast cancer, Journal of Clinical Oncology, 26, 521, 2008	
Miller, Kd, McCaskill-Stevens, W, Sisk, J, Loesch, Dm, Monaco, F, Seshadri, R, Sledge, Gw, Combination versus sequential doxorubicin and docetaxel as primary chemotherapy for breast cancer: a randomized pilot trial of the Hoosier Oncology Group, Journal of Clinical Oncology, 17, 3033-3037, 2012	Intevention outside scope of protocol - Neoadjuvant chemotherapy
Moebus, V., Jackisch, C., Lueck, H. J., du Bois, A., Thomssen, C., Kurbacher, C., Kuhn, W., Nitz, U., Schneeweiss, A., Huober, J., Harbeck, N., von Minckwitz, G., Runnebaum, I. B., Hinke, A., Kreienberg, R., Konecny, G. E., Untch, M., Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study, Journal of clinical oncology, 28, 2874-80, 2010	Comparison between different taxane regimens
Moore, H. C. F., Green, S. J., Gralow, J. R., Bearman, S. I., Lew, D., Barlow, W. E., Hudis, C., Wolff, A. C., Ingle, J. N., Chew, H. K., Elias, A. D., Livingston, R. B., Martino, S., Intensive dose-dense compared with high-dose adjuvant chemotherapy for high-risk operable breast cancer: Southwest Oncology Group/Intergroup study 9623, Journal of clinical oncology, 25, 1677-1682, 2007	Contains platinum drugs (outside scope of this review question) and ciprofloxacin (not routinely used in UK)
Muller, I., Kilburn, L. S., Taylor, P. N., Barrett-Lee, P. J., Bliss, J. M., Ellis, P., Ludgate, M. E., Dayan, C. M., TPOAb and Thyroid Function Are Not Associated with Breast Cancer Outcome: Evidence from a Large-Scale Study Using Data from the Taxotere as Adjuvant Chemotherapy Trial (TACT, CRUK01/001), European Thyroid Journal, 6, 197-207, 2017	Additional subgroup analysis for TACT that is not of interest to the committee
Nitz, U., Huober, J. B., Lisboa, B., Harbeck, N., Fischer, H., Moebus, V., Hoffmann, G., Augustin, D., Weiss, E., Kuhn, W., West German Study Group, A. G. O. Mamma, Interim results of Intergroup EC-Doc Trial: A randomized multicenter phase III trial comparing adjuvant CEF/CMF to EC- docetaxel in patients with 1-3 positive lymph nodes, Journal of Clinical Oncology, 26, 515, 2008	Abstract only
Ohsumi, S, Shimozuma, K, Ohashi, Y, Takeuchi, A, Nomura, Y, Suemasu, K, Objective and Subjective Assessment of Edema during Adjuvant Chemotherapy Using Taxane-Containing Regimens in a Randomized Controlled Trial: National Surgical Adjuvant Study of Breast Cancer (NSAS-BC) 02, 69, 2010	Abstract only
Ohsumi, S., Shimozuma, K., Ohashi, Y., Takeuchi, A., Suemasu, K., Kuranami, M., Ohno, S., Watanabe, T., Subjective and objective assessment of edema during adjuvant chemotherapy for breast cancer using taxane-containing regimens in a randomized controlled trial: The national surgical adjuvant study of breast cancer 02, Oncology, 82, 131-138, 2012	Compares different taxane regimens
Ozdemir, N., Aksoy, S., Zengin, N., Altundag, K., Taxanes in the adjuvant treatment of node-negative breast cancer patients, Journal of B.U.ON., 17, 27-32, 2012	Contains comparisons outside scope
Pajares, B., Pollan, M., Martin, M., Mackey, J. R., Lluch, A., Gavila, J., Vogel, C., Ruiz-Borrego, M., Calvo, L., Pienkowski, T., Rodriguez-Lescure, A., Segui, M. A., Tredan, O., Anton, A., Ramos, M., Camara Mdel, C.,	Obesity subgroup analysis of included trials

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
Rodriguez-Martin, C., Carrasco, E., Alba, E., Obesity and survival in operable breast cancer patients treated with adjuvant anthracyclines and taxanes according to pathological subtypes: a pooled analysis, Breast Cancer Research, 15, R105, 2013	
Petrelli, F., Borgonovo, K., Cabiddu, M., Lonati, V., Barni, S., Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: A meta-analysis, Breast Cancer Research and Treatment, 135, 335-346, 2012	Contains comparisons outside scope
Piedbois, P., Serin, D., Priou, F., Laplaige, P., Greget, S., Angellier, E., Teissier, E., Berdah, J. F., Fabbro, M., Valenza, B., Herait, P., Jehl, V., Buyse, M., Dose-dense adjuvant chemotherapy in node-positive breast cancer: Docetaxel followed by epirubicin/cyclophosphamide (T/EC), or the reverse sequence (EC/T), every 2 weeks, versus docetaxel, epirubicin and cyclophosphamide (TEC) every 3 weeks. AERO B03 randomized phase II study, Annals of Oncology, 18, 52-57, 2007	Comparison between different taxane regimens
Pippen, J., Paul, D., Vukelja, S., Clawson, A., Iglesias, J., Dose-dense doxorubicin and cyclophosphamide followed by dose-dense albumin-bound paclitaxel plus bevacizumab is safe as adjuvant therapy in patients with early stage breast cancer, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 130, 825-31, 2011	Comparison between different taxane regimens
Puhalla, S., Mrozek, E., Young, D., Ottman, S., McVey, A., Kendra, K., Merriman, N. J., Knapp, M., Patel, T., Thompson, M. E., Maher, J. F., Moore, T. D., Shapiro, C. L., Randomized phase II adjuvant trial of dose-dense docetaxel before or after doxorubicin plus cyclophosphamide in axillary node-positive breast cancer, Journal of clinical oncology, 26, 1691-7, 2008	Comparison between different taxane regimens
Qin, Y. Y., Li, H., Guo, X. J., Ye, X. F., Wei, X., Zhou, Y. H., Zhang, X. J., Wang, C., Qian, W., Lu, J., He, J., Adjuvant chemotherapy, with or without taxanes, in early or operable breast cancer: a meta-analysis of 19 randomized trials with 30698 patients, PLoS ONE [Electronic Resource], 6, e26946, 2011	Contains comparisons outside scope
Ranganathan, A, Moore, Z, O'Shaughnessy, Ja, Phase III adjuvant trial comparing dose-dense epirubicin/cyclophosphamide plus paclitaxel with doxorubicin/cyclophosphamide plus paclitaxel or cyclophosphamide/epirubicin/5-fluorouracil in women with high-risk operable breast cancer, Clinical Breast Cancer, 7, 447-9, 2007	Conference presentation
Roche, H, Allouache, D, Romieu, G, Bourgeois, H, Canon, J, Serin, D, Five-Year Analysis of the FNCLCC-PACS04 Trial: FEC100 vs ED75 for the Adjuvant Treatment of Node Positive Breast Cancer, 69, 2010	Conference presentation
Saloustros, E., Malamos, N., Boukovinas, I., Kakolyris, S., Kouroussis, C., Athanasiadis, A., Ziras, N., Kentepozidis, N., Makrantonakis, P., Polyzos, A., Christophyllakis, C., Georgoulias, V., Mavroudis, D., Dose-dense paclitaxel versus docetaxel following FEC as adjuvant chemotherapy in axillary node-positive early breast cancer: a multicenter randomized study of the Hellenic Oncology Research Group (HORG), Breast Cancer Research and Treatment, 148, 591-597, 2014	Compares different taxane regimens

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
Schneider, B. P., Zhao, F., Wang, M., Stearns, V., Martino, S., Jones, V., Perez, E. A., Saphner, T., Wolff, A. C., Sledge, G. W., Jr., Wood, W. C., Davidson, N. E., Sparano, J. A., Neuropathy is not associated with clinical outcomes in patients receiving adjuvant taxane-containing therapy for operable breast cancer, Journal of clinical oncology, 30, 3051-7, 2012	Comparison between different taxane regimens
Schonherr, A., Aivazova-Fuchs, V., Annecke, K., Juckstock, J., Hepp, P., Andergassen, U., Augustin, D., Simon, W., Wischnik, A., Mohrmann, S., Salmen, J., Zwingers, T., Kiechle, M., Harbeck, N., Friese, K., Janni, W., Rack, B., Toxicity analysis in the ADEBAR trial: Sequential anthracycline-taxane therapy compared with FEC120 for the adjuvant treatment of high-risk breast cancer, Breast Care, 7, 289-295, 2012	Includes same outcomes and population as Janni 2016 but with shorter follow-up
Shao, N., Wang, S., Yao, C., Xu, X., Zhang, Y., Lin, Y., Sequential versus concurrent anthracyclines and taxanes as adjuvant chemotherapy of early breast cancer: A meta-analysis of phase III randomized control trials, Breast, 21, 389-393, 2012	Insufficient information about included studies
Skarlos, P., Christodoulou, C., Kalogeras, K. T., Eleftheraki, A. G., Bobos, M., Batistatou, A., Valavanis, C., Tzaida, O., Timotheadou, E., Kronenwett, R., Wirtz, R. M., Kostopoulos, I., Televantou, D., Koutselini, E., Papaspirou, I., Papadimitriou, C. A., Pectasides, D., Gogas, H., Aravantinos, G., Pavlidis, N., Arapantoni, P., Skarlos, D. V., Fountzilas, G., Triple-negative phenotype is of adverse prognostic value in patients treated with dose-dense sequential adjuvant chemotherapy: a translational research analysis in the context of a Hellenic Cooperative Oncology Group (HeCOG) randomized phase III trial, Cancer Chemotherapy & Pharmacology, 69, 533-46, 2012	Insufficient presentation of results
Smith, Re, Brown, Am, Mamounas, Ep, Anderson, Sj, Lembersky, Bc, Atkins, Jh, Shibata, Hr, Baez, L, DeFusco, Pa, Davila, E, Tipping, Sj, Bearden, Jd, Thirlwell, Mp, Randomized trial of 3-hour versus 24-hour infusion of high-dose paclitaxel in patients with metastatic or locally advanced breast cancer: national Surgical Adjuvant Breast and Bowel Project Protocol B-26, Journal of Clinical Oncology, 17, 3403-3411, 2012	Population outside scope: majority of patients had stage IV disease
Sparano, Ja, Zhao, F, Martino, S, Ligibel, Ja, Perez, Ea, Saphner, T, Wolff, Ac, Sledge, Gw, Wood, Wc, Davidson, Ne, Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 33, 2353-60, 2015	Comparison between different taxane regimens
Spigel, Dr, Hainsworth, Jd, Burris, Ha, Molthrop, Dc, Peacock, N, Kommor, M, Vazquez, Er, Greco, Fa, Yardley, Da, A pilot study of adjuvant doxorubicin and cyclophosphamide followed by paclitaxel and sorafenib in women with node-positive or high-risk early-stage breast cancer, Clinical advances in hematology & oncology, 9, 280-6, 2011	Non-RCT
Swain, S. M., Jeong, J., Geyer, C. E., Costantino, J. P., Pajon, E. R., Fehrenbacher, L., Atkins, J. N., Polikoff, J., Vogel, V. G., Erban, J. K., Livingston, R. B., Perez, E. A., Mamounas, E. P., Ganz, P. A., Land, S. R., Wolmark, N., NSABP B-30: Definitive analysis of patient outcome from a randomized trial evaluating different	Abstract only

Excluded studies - RQ5.1 Which people with early and locally advanced breast cancer would benefit from the addition of taxanes to anthracycline based adjuvant chemotherapy?	
Study	**Reason for exclusion**
schedules and combinations of adjuvant therapy containing doxorubicin, docetaxel and cyclophosphamide in women with operable, node-positive breast cancer, Cancer Research, 69, no pagination, 2009	
Swain, S. M., Tang, G., Geyer Jr, C. E., Rastogi, P., Atkins, J. N., Donnellan, P. P., Fehrenbacher, L., Azar, C. A., Robidoux, A., Polikoff, J. A., Brufsky, A. M., Biggs, D. D., Levine, E. A., Zapas, J. L., Provencher, L., Northfelt, D. W., Paik, S., Costantino, J. P., Mamounas, E. P., Wolmark, N., Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31, 3197-3204, 2013	Compares different taxane regimens
Swain,S.M., Land,S.R., Ritter,M.W., Costantino,J.P., Cecchini,R.S., Mamounas,E.P., Wolmark,N., Ganz,P.A., Amenorrhea in premenopausal women on the doxorubicin-and-cyclophosphamide-followed-by-docetaxel arm of NSABP B-30 trial, Breast Cancer Research and Treatment, 113, 315-320, 2009	Compares different taxane regimens
Watanabe, T., Kuranami, M., Inoue, K., Masuda, N., Aogi, K., Ohno, S., Iwata, H., Mukai, H., Uemura, Y., Ohashi, Y., Comparison of an AC-taxane versus AC-free regimen and paclitaxel versus docetaxel in patients with lymph node-positive breast cancer: Final results of the National Surgical Adjuvant Study of Breast Cancer 02 trial, a randomized comparative phase 3 study, Cancer, 123, 759-768, 2017	Compares different taxane regimens
Wilcken, N. R. C., Stockler, M. R., Individual patient meta-analysis: Taxane plus anthracycline reduces mortality from early breast cancer, Annals of Internal Medicine, 156, 432-444, 2012	Insufficient information
Wildiers, H, Dirix, L, Neven, P, Provâ□š, A, Clement, P, Amant, F, Chemotherapy dose delays and dose reductions in breast cancer patients receiving dose-dense FEC and docetaxel - results of a randomized, open-label phase II study, 2007	Conference abstract
Wildiers, H., Dirix, L., Neven, P., Prove, A., Clement, P., Squifflet, P., Amant, F., Skacel, T., Paridaens, R., Delivery of adjuvant sequential dose-dense FEC-Doc to patients with breast cancer is feasible, but dose reductions and toxicity are dependent on treatment sequence, Breast Cancer Research & Treatment, 114, 103-12, 2009	Compares different taxane regimens
Williams, Chris, Bryant, Andrew, Short versus long duration infusions of paclitaxel for any advanced adenocarcinoma, Cochrane Database of Systematic Reviews, 2011	Comparisons outside scope
Yardley, D. A., Arrowsmith, E. R., Daniel, B. R., Eakle, J., Brufsky, A., Drosick, D. R., Kudrik, F., Bosserman, L. D., Keaton, M. R., Goble, S. A., Bubis, J. A., Priego, V. M., Pendergrass, K., Manalo, Y., Bury, M., Gravenor, D. S., Rodriguez, G. I., Inhorn, R. C., Young, R. R., Harwin, W. N., Silver, C., Hainsworth, J. D., Burris, H. A., TITAN: phase III study of doxorubicin/cyclophosphamide followed by ixabepilone or paclitaxel in early-stage triple-negative breast cancer, Breast Cancer Research and Treatment, 164, 649-658, 2017	Includes ixabepilone - not used in UK
Yardley, Da, Hart, L, Badarinath, S, Waterhouse, Dm, Daniel, B, ChildsBh,, Preliminary results of a multicenter study of bevacizumab with 3 docetaxel-based adjuvant breast cancer regimens, 2007	Conference abstract

1 *RCT, randomised controlled trial*

Economic studies

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

4

Appendix L – Research recommendations

No research recommendations were made for this review question.

Appendix M – Nominal group technique questionnaire for adding taxanes to anthracycline-based chemotherapy regimens for elderly people and for those with cardiac disease

Name:										
Age										
	Strongly disagree								**Strongly agree**	**Insufficient knowledge**
1. There are higher rates of haematological toxicities associated with taxane use among older patients compared with younger patients	1	2	3	4	5	6	7	8	9	☐
Comments:										
2. Three weekly docetaxel is not appropriate for elderly patients with early breast cancer	1	2	3	4	5	6	7	8	9	☐
Comments:										
3. There should not be age restrictions associated with weekly paclitaxel	1	2	3	4	5	6	7	8	9	☐
Comments:										
4. Taxane-containing chemotherapy regimens are feasible in older patients	1	2	3	4	5	6	7	8	9	☐
Comments:										

5. Age itself is a less important determinant of the appropriateness of taxane-containing chemotherapy than physical health and functional status	1	2	3	4	5	6	7	8	9	☐
Comments:										
Cardiac disease										
	Strongly disagree								**Strongly agree**	**Insufficient knowledge**
6. The absolute cardiac risks associated with taxanes are unknown	1	2	3	4	5	6	7	8	9	☐
Comments:										
7. Taxane-containing regimens may reduce cardiac toxicity if their inclusion results in lower cumulative anthracycline exposure	1	2	3	4	5	6	7	8	9	☐
Comments:										
8. Taxanes may increase the cardiac toxicity effect of anthracyclines	1	2	3	4	5	6	7	8	9	☐
Comments:										
9. Paclitaxel may increase heart failure when combined with doxorubicin	1	2	3	4	5	6	7	8	9	☐
Comments:										

10. Cardiac risks associated with paclitaxel are greater than those associated with docetaxel	1	2	3	4	5	6	7	8	9	☐
Comments:										
11. Existing cardiac disease may impact ability to cope with side effects of taxane chemotherapy	1	2	3	4	5	6	7	8	9	☐
Comments:										
Re-rated statements (Round 2)										
	Strongly disagree								**Strongly agree**	**Insufficient knowledge**
12. Physical health and functional status should be considered in addition to age when deciding the appropriateness of taxane-containing chemotherapy	1	2	3	4	5	6	7	8	9	☐
Comments:										

1
2

Appendix N – Nominal group technique results

Table 49: Nominal group technique consensus ratings for adding taxanes to anthracycline-based chemotherapy regimens for elderly people and for those with cardiac disease

Area	Statement no.	Statement	Agreement (%)	Action
Age	1	There are higher rates of haematological toxicities associated with taxane use among older patients compared with younger patients	50	Discarded as less than 60% agreement
	2	Three weekly docetaxel is not appropriate for elderly patients with early breast cancer	67	Discarded – committee agreed that this is better captured by statement 5
	3	There should not be age restrictions associated with weekly paclitaxel	100	Used to inform recommendation
	4	Taxane-containing chemotherapy regimens are feasible in older patients	100	Used to inform recommendation
	5	Age itself is a less important determinant of the appropriateness of taxane-containing chemotherapy than physical health and functional status	75	Re-drafted and re-rated.
Cardiac disease	6	The absolute cardiac risks associated with taxanes are unknown	0	Discarded as less than 60% agreement
	7	Taxane-containing regimens may reduce cardiac toxicity if their inclusion results in lower cumulative anthracycline exposure	80	Used to inform recommendation
	8	Taxanes may increase the cardiac toxicity effect of anthracyclines	20	Discarded as less than 60% agreement
	9	Paclitaxel may increase heart failure when combined with doxorubicin	0	Discarded as less than 60% agreement
	10	Cardiac risks associated with paclitaxel are greater than those associated with docetaxel	0	Discarded as less than 60% agreement
	11	Existing cardiac disease may impact ability to cope with side effects of taxane chemotherapy	100	Used to inform recommendation

Area	Statement no.	Statement	Agreement (%)	Action
Re-rated statements	5 (round 2)	Physical health and functional status should be considered in addition to age when deciding the appropriateness of taxane-containing chemotherapy	100	Used to inform recommendation

1