Supplemental Materials for

Adjuvant chemotherapy for early female breast cancer: A systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline

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Supplemental Table 1. Antimetabolites: CMF, capecitabine, and gemcitabine.

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Amadori, 2008[1] Update of Amadori, 2000[2]	1989−1993	CMF×6 or none after locoregional therapy (mastectomy or quadrantectomy + RT)	278	N0 (at least 10 nodes examined), high thymidine labeling index (TLI) ≥3.1%, age ≤70 y	64% ≤2 cm (Stage I)	42% premenopausal, 65% ER+, 50% PR+	Stratified pts according to cell proliferation evaluated by TLI	TLI 3.1%−4.4% (33.1% of pts), TLI 4.5−6.8% (33.8%), TLI >6.8 (33.1%) Relapse at median follow-up of 12 y, CMF vs control: Overall: HR=0.75 (95% CI 0.50−1.13), p=0.17, (NS) Pts who received full CMF dose: HR=0.59 (95% CI 0.36−0.95), p=0.03 TLI 3.1%−4.4%: HR=1.05 (95% CI 0.45−2.49), p=0.91 TLI 4.5%−6.8%: HR=0.30 (95% CI 0.12−0.72), p=0.01 TLI>6.8 %: HR=0.79 (95% CI 0.37−1.68), p=0.53, 25% of relapses occurred within 20 mo in control and within 93 mo in CMF group Death at median follow-up of 12 y, CMF vs control Overall: HR=0.80 (95% CI 0.48−1.33), p=0.38 Pts who received full CMF dose: HR=0.57 (95% CI 0.31−1.07), p=0.08 TLI 3.1%−4.5%: HR=0.86 (95% CI 0.29−2.57), p=0.78 TLI 4.5%−6.8%: HR=0.27 (95% CI 0.08−0.83), p=0.02 TLI>6.8 %: HR=0.71 (95% CI 0.30−1.73), p=0.46
Taucher, 2008[3] 1991−1999	ABCSG-07	CMF timing: CMF×3 preoperative vs CMF×3 post-operative All received additional therapy determined by histological nodal status (3×CMF if N0 or 3×EC if N+) All had axillary dissection,	398	HR−1991−99; high-risk (N1) HR+ 1996−99	24% T1, 65% T2, 9% T3; N0−1, M0	9% ER+, 15% PR+ 64% N0, 49% premenopausal	Biopsy proven cancer and/or cN+	OS not affected by therapy group: HR=0.800 (95% CI 0.563−1.136), p=0.213 Recurrence after median follow-up 9 y: RFS: HR=0.7 (95% CI 0.52−0.96), p=0.024 favouring postop treatment, although rates of local recurrence (13.3 vs 8.2%, p=0.1) and distant metastases (30.5% vs 22.6%, p=0.07) for pre and postoperative groups were not

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		BCS +RT or modified radical mastectomy (+RT at physician's discretion)						significantly different
Muss, 2009[4]	CALGB 49907 2001−2006	Std chemotherapy (CMF×6 or AC×4) vs capecitabine×6 Axilla treated at discretion of patient and surgeon HR+ offered tamoxifen or AI after chemotherapy Trastuzumab recommended in last year (2006) for HER2+ tumours	633 (ended early due to safety)	Age ≥65 y	I, II, IIA, IIIB; >1 cm	10% HER2+, 67% HR+, 70% N+, 55% >2 cm	Operable, histologically confirmed adenocarcinoma	At median follow-up of 2.4 y: • RFS: 80% capecitabine, 89% std chemotherapy • OS: 88% capecitabine, 93% std chemotherapy Estimated at 3 y: • RFS: 68% capecitabine, 85% std chemotherapy, HR=2.09, p<0.001 • OS: 86% capecitabine, 91% std chemotherapy; HR=1.85, p=0.02 • HR− subgroup with capecitabine vs all others: risk of relapse HR=4.39 (95% CI 2.9−6.7, p<0.001); risk of death HR=3.76 (95% CI 2.23−6.34, p<0.001) • Adverse effects (grade 3−4 events): 70% CMF, 60% doxorubicin, 34% capecitabine • Adverse effects (hematological grade 3−4 effects): 52% CMF, 54% doxorubicin, 2% capecitabine
Kornblith, 2011[5]	CALGB 49907 2001−2006	See preceding entry (QoL substudy)	350					Pts with capecitabine had significantly better QoL, role function, social function, appetite, and less systemic adverse effects, psychological distress, fatigue, nausea, vomiting or constipation; capecitabine was worse for hand-foot syndrome and diarrhea. QoL similar at 1 y. Concluded std chemotherapy is better than capecitabine to improve RFS and OS, and survival rate effects outweigh short-term adverse effects

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Ejlertsen, 2010[6]	DBCG 77B 1977−83	CMF (N=423) vs cyclophosphamide (N=424) vs levamisole (N=112) vs no adjuvant systemic therapy (RT only, N=187) CMF was oral C at 80 mg/m^2 on days 1−14, IV M at 30 mg/m^2 and F at 500 mg/m^2 on days 1−8; q28d×12); C only as for CMF but 130 mg/m^2; levamisole 5 mg/w×48 w All received radiotherapy to chest wall and regional lymph nodes Endocrine therapy not permitted	1146	Premenopausal; N+ or >5 cm or invasion of deep fascia with no distant metastasis	high-risk; 17% N0, 56% N1, 27% N2+; 25% T1, 37% T2, 13 % T3, 24% unknown	hormone receptor status unknown for 70% of pts; 22% HR+	All had mastectomy + axillary sampling or clearance before chemotherapy	Levamisole arm closed early (1979) due to adverse effects, and resulted in closure of control arm as well in 1981 10−y survival rates: CMF 62%, C 60%, L 41%, Control 46%; C vs control: HR=0.70, p=0.02; CMF vs control: HR=0.70, p=0.02, C vs CMF: no difference (HR=1.11, p=0.32) Invasive DFS: CMF 49%, C 56%, L 35%, Control 39% OS benefit persisted at 25−y follow-up when adjusted for baseline characteristics: C vs control: HR=0.66, p=0.002; CMF vs control: HR=0.59, p=0.0001
Ejlertsen, 2008[7,8]	DBCG 77B, 82B, 89B, 89D Results of all studies previously reported separately 1977−2001	Retrospective unplanned cross-trial comparison of higher-dose classic vs lower-dose IV CMF (CMF +RT dose and schedule) • **DBCG 77B**: see Ejlertsen 2010; used classic CMF • **DBCG 82B**: CMF +RT, CMF, CMF + tamoxifen • (IV CMF at 600, 40, 600 mg/m^2 q4w×8 except with delay after first cycle to administer RT) • **DBCG 89B**: HR+: RT + OA vs RT +CMF (CMF q3w×9) • **DBCG 89D**: HR−: RT + CMF vs RT + CEF; (CMF q3w×9); secondary	5652 (2113 received CMF + RT)	Premenopausal, N+	65% N1, 27% N2, 8% N3 43% T1 44% T2 9% T3		Data on those administered CMF combined from 4 studies of DBCG, N+ data only, exclude those on tamoxifen or OA	10−y survival rates after CMF were 48% with classic CMF, 45% administered every 4 w, 47% administered every 3 w; after adjusting in multivariate analysis was 30 % increase in risk of recurrence in 3− or 4−weekly regimen compared with classic CMF Effect was age dependent (p<0.01): pts aged <40 y did better in the 77 cohort, whereas those aged >50 y did better in 89 cohort, authors suggested may be endocrine effect because for those aged <40 y classic CMF resulted in 15% regular menses, whereas this was 47% in the 89 cohort; interpret with caution due to non-experimental design

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		randomization to pamidronate for 4 y permitted.						
Joensuu, 2012[9]	FinXX, NCT00114816 2004−2007	Capecitabine TX×3→ CEX×3 vs T×3→ CEF×3	1500	N+ (89%), or N0 if >20 mm and PR− (11%)	44% pT1, 50% pT2, 5% pT3; [mostly IIA−IIB]	77% ER+, 62% PR+, 19% HER2+	Histologically confirmed invasive, excluded if had neoadjuvant chemotherapy	5−y RFS 87% for TX/CEX vs 84% for T/CEF, HR=0.79 (95% CI 0.60 to 1.04), p=0.087 56 pts assigned to TX→ CEX died during the follow-up compared to 75 pts assigned to T→ CEF, HR=0.73 (95% CI 0.52−1.04), p=0.08 In exploratory (subgroup) analyses, TX→ CEX improved breast cancer-specific survival rate (HR=0.64, p=0.027) and RFS rates (HR=0.64, 95% CI 0.43−0.96) in female pts with triple-negative disease and in female pts who had >3metastatic axillary lymph nodes at the time of diagnosis
Canney 2012, 2014[10-12] Velikova 2014[13] [abstracts only]	TACT2, CRUK/05/019 2005−2008	Accelerated E (aE) + pegfilgrastim vs E; then X vs classic CMF E-CMF is control	4371 female pts, 20 men	N+ or high risk N0 invasive early breast cancer			1 y trastuzumab if HER2+; 5 y endocrine therapy if HR+	• Median follow-up 61 mo, X vs CMF: • TTR events: 14.0% vs 14.4%, HR=0.98 (95% CI 0.84−1.15),p=0.79 • OS: HR=1.00 (95% CI 0.84−1.20) • DFS: HR0.99 (95% CI 0.86−1.15) • Fewer serious adverse effects (except diarrhea and PPE) and better global QoL with X than CMF • Concluded X non-inferior efficacy but

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								superior tolerability • Median follow-up of 49 mo, aE vs E • TTR: 3−y recurrence rates 91.0% vs 90.9%, 5−y recurrence rates 86.4% vs 85.2%; HR=0.96 • OS 94.4% vs 95.4% at 5 y (p=0.23) • After 4 cycles, more nausea, vomiting, appetite loss, constipation, systemic adverse effects and deterioration of functioning (global QoL, role function) with aE than E, but these did not persist to 12 or 24 mo. • At end of 8 cycles, CMF had more adverse effects than with X (fatigue, dyspnea, insomnia, constipation, systemic side-effects, deterioration of functioning) and these (e.g., fatigue) often persisted to 24 mo • Impact on menstruation assessed at 18 mo for premenopausal aged <50 y (N=1622): E→ X has lower risk of permanent loss of menstrual function than E→ CMF (28% vs 69%); aE vs E had more short-term amenorrhea but effect lost by 18 m
Ohno 2013[14]		Neoadjuvant FEC then randomized to TX vs T	477	Operable, age 20−70 y; T1C−3, N0, M0 >1 cm; or T1−3, N1, MO	43% IIA, 45% IIB, 11% IIIA	Excluded pts with disease progression on FEC	Relative dose intensity of T was lower in TX group due to adverse effects	Powered for pCR difference pCR 23% vs 24% (p=0.748) At median follow-up 4.5 y, 3−y DFS rates 92.7% vs 90.7%, HR=0.910 (95% CI 0.551−1.502); OS HR=0.671 (95% CI 0.303−1.488)
Pippen, 2011[15] O'Shaughnessy, 2010[16] [abstract]	US Oncology 1062 USON 01062 2002−2006	AC→ T vs AC→ TX AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 AC→ TX: AC as in other arm→ TX	2611	Resectable, early, high risk (N+, T1−3; or N0, T2+; or N0, >1 cm, HR−)			Tamoxifen or AI for 5 y if HR+; After 2005, HER2+ offered 1 y trastuzumab	Median follow-up of 5 y, 304 events DFS: HR=0.84 (95% CI 0.67−1.05), p=0.125 [endpoint not met] Distant DFS favoured TX group: HR=0.80 (95% CI 0.63−1.02), p=0.067 OS: improvement with TX vs T: HR=0.68 (95% CI 0.51−0.92), p=0.011

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		(T: 75 mg/m^2 day 1, X: 825 mg/m^2 bid, days 1−14;) [4 cycles ?]						Subgroup analysis appeared to favour TX over T Unplanned subset analysis of Ki-67 expression and DFS suggests benefit of X in more highly proliferative tumours (for Ki-67 >10%, hazard ratio for TX vs T is HR=0.70 (95% CI 0.50−0.98) for DFS and HR=0.52 (95% CI 0.33−0.82) for OS Adverse events similar in both arms, except grade 3 hand-foot syndrome (3.8% T vs 18.1% TX), grade 3/4 stomatitis (4.5% vs 9.1%), diarrhea (2.9% vs 5.1%), and febrile neutropenia (13.1% vs 9.4%)

O'Shaughnessy, 2012[17] [abstract]	USON 01062	See previous entry in table				2195 ductal
						355 lobular or mixed
								Exploratory analysis by histology:
								• ductal pts AC→ T vs AC→ XT:
								  • no difference in DFS (HR=0.92, p=0.48) or OS (HR=0.75, p=0.07)
								• lobular/mixed AC→ XT vs AC→ T
								  • DFS, HR=0.55, p=0.055
								  • OS, HR=0.38, p=0.04

Bermejo, 2013[18]	GEICAM/2003−10 2004−2007	ET→ X vs EC→ T ET (90/75 mg/m^2)q3w×4→ X (1250 mg/m^2 bid d1−14) q3w×4 EC (90/600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4	1384	T1−3/N1−3 operable	66% N1, 25% N2, 9% N3	Stratified by site, menopausal status, number of nodes (1−3, 4−9, 9+), hormone receptor status	HER2+ pts excluded after first 803 pts recruited; 84% HR+, 11% HER2+	After median follow-up 6.6 y, survival rates at 5 y: • DFS: 82% EC→X vs 86% EC→T, HR=1.314 (95% CI 1.042−1.657), p=0.0208 • OS not different: HR=1.113 (95% CI 0.809−1.531), p=0.511 EC→X vs EC→T : Neutropenia 10% vs 19%, hand-foot syndrome 20% vs 2%, diarrhea 11% vs 3%
Watanabe, 2009[19]	N-SAS BC 01 1996−2001	Oral uracil and tegafur (UFT) daily for 2 y vs CMF×6	707	N0, Stage I−IIIA	42% T1, 54% T2, 5% T3 [96% Stage	62% ER+ and/or PR+; 42% premenopausal	Authors considered "high risk" but no reason reported	RFS at 5 y: 88.0% CMF vs 87.8% UFT, HR=0.98 (95% CI 0.66−1.45), p=0.92 OS: 96.0% vs 96.2%, HR=0.81 for OS (95% CI 0.44 to 1.48), p=0.49 The adverse effects profiles differed between the two groups

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					I−IIA]			QoL scores were better for pts administered UFT than for those administered CMF ($p<0.05$ for social functioning, nausea/vomiting, constipation, systemic adverse effects, hair loss)
Hara 2012[20] [abstract]	N-SAS BC 01	See previous entry in table Subgroup of older pts (aged ≥65 y)	97					5−y RFS (UFT vs CMF): 93.0% vs 92.5%, HR=1.07 (95% CI 0.31−3.55) OS: 97.7% vs 98.1%, HR=1.07 (95% CI 0.15−10.25) Grade 3/4 leukopenia 0% vs 3.8%, neutropenia 4.8% vs 13.5%; grade 3/4 increased liver enzyme and nausea/vomiting less frequent with UFT; more elevated bilirubin and diarrhea observed in UFT arm; UFT better QoL scores
Ejlertsen, 2013[21]	DBCG 82c 1982−1990	CMF (IV×9) + tamoxifen vs tamoxifen (30 mg/d for 1 y)	1445	Postmenopausal ;N+, deep invasion, or >5 cm		55% N1, 34% N2+ 37% T1, 50% T2, 12% T3	Mastectomy + axillary sampling or clearance (level 1 + part of level II)	Analysis 20 y after recruitment closed; median follow-up 10 y DFS, 24 y OS DFS (CMFT vs CMF): HR=0.89 (95% CI 0.78−1.01), p=0.08 [ITT] DFS adjusted: HR=0.82 (95% CI 0.71−0.93), p=0.003 OS: no difference, HR=0.96 (95% CI 0.86−1.08), p=0.51
Colleoni 2011[22] [abstract]	IBCSG 22−00	Study of low-dose maintenance/metronomic CM after surgery + chemo -Randomized to 12 mo CM vs no CM	1080 planned	ER−PR− (<10%), known HER2 status		Stratified by menopausal status, induction regimen	Concurrent trastuzumab permitted if HER2+	Ongoing
Wardley, 2008[23]	tAnGo 2000−	EC→ G + P vs EC→ P E 90 mg/m^2 + C 600 mg/m^2 q3w×4→ [P 175 mg/m^2 q3h infusion day 1 and G 1250 mg/m^2 days 1 and 8] q3 w×4	3000		Substudy: 19% N0 35% N1 46% N2+	Substudy: 20% ER+ 15% PR+		Ongoing, no survival rate results

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Earl, 2014[24]	Neo-tAnGo	Neoadjuvant: EC→ P vs P→ EC vs EC→ PG vs PG→ EC Effect of gemcitabine and role of sequence (EC→ P vs P→ EC) Stratified by ER status, tumour size (50 mm cut-off), nodal status (N0/N+), inflammatory/locally advanced (yes/no)	831	Early invasive, >2 cm; no previous chemo, RT, endocrine therapy T4 eligible	80% T2, 20% T3 50% N+	67% ER+ 51% PR+ 25% inflammatory or LABC; 57% premenopausal, 5% perimenopausal		Median follow-up 47 mo; first planned interim analysis found no significant difference in DFS or OS • DFS : EC→ P vs EC→ PG, HR=1.13 (95% CI 0.88−1.46), p=0.34 • DFS: P→ EC vs EC→ P, HR=0.84 (95% CI 0.65−1.09), p=0.18 • OS: EC→ P vs EC→ PG, HR=1.02 (95% CI 0.76−1.39), p=0.89 • OS: P→ EC vs EC→ P, HR=0.82 (95% CI 0.60−1.11), p=0.19 • pCR greater with P→ EC than EC→ P (20% vs 15%, p=0.03); G did not increase pCR • pCR was correlated with significant improvement in DFS (p<0.0001) and OS (p=0.0007)
Toi, 2012[25] [abstract]	OOTR N0003	Neoadjuvant study FEC→ TX vs FEC→ T	504	Operable, T1C−3N0M0/ T1−3N1M0		Median 3.5 cm, 56% N+		Discontinued in 22% TX and 5% T groups (p<0.0001) Median follow-up 3.7 y, DFS 92% TX vs 91% T, HR=0.907 (95% CI 0.528−1.557), p=0.723 More hand-foot syndrome with TX (15% vs 2%) Concluded adding X to T not superiority to T alone following FEC
Schneeweiss 2011[26]	2005−2007	Pemetrexed×4 vs cyclophosphamide×4 Doxorubicin + pemetrexed→ docetaxel vs doxorubicin + cyclophosphamide→ docetaxel	257	Operable T2−T4a−c, N0−2, M0	30% IIA, 46% IIB, 17% IIIA, 8% IIIB 39% N0 6% T1 38% T2 37% T3	66% HR+ 15% HER2+		Ongoing, no survival rate results

Abbreviations: AC, doxorubicin + cyclophosphamide; aE, accelerated epirubicin; AI, aromatase inhibitor; BCS, breast-conserving surgery; C, cyclophosphamide; CEF, cyclophosphamide + epirubicin+ fluorouracil; CEX, cyclophosphamide + epirubicin + capecitabine; CMF, cyclophosphamide + methotrexate + fluorouracil; DFS, disease-free survival rate; E, epirubicin; ER, estrogen receptor; EC, epirubicin + cyclophosphamide; F, 5−fluorouracil; FEC, fluorouracil + epirubicin + cyclophosphamide; G, gemcitabine; HR+, hormone receptor positive; HR−, hormone receptor negative; IDFS, invasive disease-free survival rate; ITT, intention to treat; LABC, locally advanced breast cancer; M, methotrexate; N0, node-negative; N+, nod-positive; OA, ovarian ablation; OS, overall survival rate; P, paclitaxel; pCR, pathologically complete response; PG, paclitaxel + gemcitabine; pts, patients; PR, progesterone receptor; QoL, quality of life; RFS, recurrence-free survival rate; RT, radiation therapy; T, docetaxel (Taxotere); TTR, time to recurrence; TX, docetaxel + capecitabine; TLI, thymidine labeling index; UFT, oral uracil and tegafur; X, capecitabine

* HER2, ER/PR, risk, menopausal status

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Supplemental Table 2. Anthracyclines: Doxorubicin and epirubicin.

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de Azambuja, 2009[27]	1988−1996	CMF vs EC vs high-dose EC (HEC) CMF×6 vs EC×8 vs HEC×8	777	N+ (≥10 nodes resected), age ≤70 y, operable breast cancer (mastectomy or lumpectomy + ALND)	60 % N1, 40% N2+ 43% pT1, 39% pT2, 2% pT3, 16% unknown	54% ER+, 30% ER−, 16% unknown; 58% premenopausal	Tamoxifen for 5 y if ER+ or unknown and postmenopausal; RT after BCS; PMRT depended on centre's policy	• 15−y EFS was 45% for CMF, 39% for EC, 50% for HEC • HEC vs EC: HR=0.77 (95% CI 0.60−0.98), p=0.03 • HEC vs CMF: HR=0.90 (95% CI 0.7−1.15), p=0.39 • EC vs CMF: HR=0.86 (95% CI 0.67−1.09), p=0.21 • No difference in OS • Cardiac adverse effects more frequent with HEC than with CMF(p=0.006) but not more than with EC (p=0.21)
Kimura, 2010[28]	1996−2000	CEF vs CMF post-surgery	294	N+, ALND, no previous systemic therapy or RT, exclude BCS	I−IIIA: 68% II, 25% IIIA; 32% N1, 42% N2, 26% N3; 11% T1, 64% T2, 17% T3	61% premenopausal, 53% ER+, 48% PR+	Tamoxifen for 2 y if ER+ or ER unknown; did not meet intended sample size of 700	• 5−y survival rate 77.1% for CEF and 71.4% for CMF, HR=0.79 (95% CI 0.50−1.24), p=0.24 • 5−y DFS 55.7% for CEF and 48.9% for CMF, HR=0.80 (95% CI 0.57−1.12), p=0.15 • Adverse drug reactions more common with CEF • Study had insufficient power to prove significance of trends
Amadori, 2011[29]	1997−2004	E→ CMF vs CMF→ E (after radical resection)	878	Rapidly proliferating breast cancer (TLI >3% or histological grade 3 or S phase >10% or Ki-67 >20%); N1 or N0 and >1 cm	53% N0, 23% N1, 13% N2, 10% N3; 49% pT1, 46% pT2, 5% pT3−4	47% premenopausal, 62% ER+, 50% PR+, 44% HER2+	ER+ received tamoxifen for 5 y after chemotherapy, GnRH optional in premenopausal pts not achieving amenorrhea; RT administered after BCS; PMRT for pT3−4 tumours	At a median follow-up of 69 m: • 5−y OS 91% (88%−94%) for E→ CMF and 93% (90%−95%) for CMF→ E, with adjusted HR=0.88 (95% CI 0.58−1.35) • DFS 80% in both arms, adjusted HR=0.99 (95% CI 0.73−1.33) • Adverse events were similar, apart from a higher rate of neutropenia in the CMF→ E arm (12% vs 7. 5%, p=0.03). • No important differences in clinical outcome were observed between the two different sequences, making both a valid option in early breast cancer

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Rocca 2014[30]		See previous entry in table Amadori[29] E→ CMF vs CMF→ E vs CMF×6 (E×4 and CMF×4)	1066 (705 analyzed)				Combined E→ CMF and CMF→ E arms (E/CMF) Post-hoc analysis by tumour biomarkers HR, Ki-67, HER2 for 705 pts	E/CMF arms vs CMF: • DFS: 84% vs 73%, HR=0.54, p=0.0006 • OS: 94% vs 87%, HR=0.44, p=0.0009 Subgroup DFS, E/CMF vs CMF alone: •Ki-67 low: 89% vs 85%, HR=0.55, p=0.116 •Ki-67 high: 82% vs 68%, HR=0.53, p=0.002 •HER2−: 86% vs 74%, HR=0.50, p=0.001 •HER2+: 81% vs 71%, HR=0.64, p=0.147 •ER+: 86% vs 81%,, HR=0.61, p=0.047 •ER−: 81% vs 63%, HR=0.51, p=0.008 •PR+: 88% vs 82%, HR=0.65, p=0.151 •PR−: 81% vs 65%, HR=0.51, p=0.002 •ER+ and/or PR+: 85% vs 80%, HR=0.61, p=0.036 •Triple Negative: 85% vs 55%,, HR=0.33, p=0.0007 •ER−PR−HER2+: 75% vs 71%,, HR=1.10, p=0.840 •ER−PR−Ki-67 >20%: 82% vs 58%, HR=0.45, p=0.005
Cheang, 2012[31]	NCIC.CTG MA.5 1989−1993	CEF + antibiotic prophylaxis vs CMF Prognostic impact of intrinsic subtype and interaction with treatment; determined by PAM50 gene-expression test	716	Premenopausal, N+	39% T1, 49% T2, 5% T3, 7% unknown 61% N1, 39% N2+		60% ER+, 28% ER−, 12% ER unknown 20% HER2+, 80% HER2− (HER2 measured only in subset with PAM50 test) <u>PAM50 determined Intrinsic subtype (N=476)</u> HER2−E (HER2 enriched) 22%	Multivariable regression results for intrinsic subgroups determined by PAM50, adjusted for clinicopathological variables •**Overall, CEF vs CMF (N=454)** •RFS: HR=0.87 (95% CI 0.67−1.12) •OS: HR=0.98 (95% CI 0.74−1.31) •**HER2−E** (N=105) •RFS HR=0.56 (95% CI 0.34−0.93) •OS HR=0.62 (95% CI 0.36−1.05) •**Non-HER2−E (N=350)** •RFS HR=1.02 (95% CI 0.76−1.38) •OS HR=1.22 (95% CI 0.86−1.74) •**Basal (N=94)** •RFS HR=1.12 (95% CI 0.60−2.08) •OS HR=1.32 (95% CI 0.71−2.46) •**Non-basal (N=361)**

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
							Basal-like 20% Luminal B 23% Luminal A 31% Normal 4%	• RFS HR=0.80 (95% CI 0.60−1.06) • OS HR=0.90 (95% CI 0.65−1.25) • **Luminal B (N=110)** • RFS HR=0.76 (95% CI 0.47−1.24) • OS HR=0.83 (95% CI 0.46−1.50) • **Luminal A (N=145)** • RFS HR=1.14 (95% CI 0.70−1.88) • OS HR=1.71 (95% CI 0.91−3.22) • HER2−E and HER2+ status strongly predicted anthracycline sensitivity, HER2+/HER2−E: 62% response to CEF, 22% response to CMF, p=0.0006
Bartlett, 2010[32] Poole, 2006[33]	NEAT, BR9601 1996−2001	E→ CMF vs classic CMF (NEAT) E→ modified CMF vs modified CMF (BR9601) Prospectively planned analysis of 1941 tumours by tissue microarrays for HER2, TOP2A, HER1−3, Ki-67, Ch17CEP (chromosome 17 centromere enumeration probe)	2391 (2021 NEAT, 370 BR9601)		28% N0 47% N1 25% N2−3 43% T1 50% T2 5% T3	48% premenopausal 9% perimenopausal 37% postmenopausal 6% unknown 50% ER+, 32% ER−, 18% unknown	Analyzed 1762 pts	Survival rate data reported in earlier publication[33], RFS and OS significantly higher with E-CMF: • 2−y RFS 91% vs 85%, 5−y RFS 76% vs 69% • 2−y OS 95% vs 92%, 5−y OS 82% vs 75%, p<0.001 for all • RFS HR=0.69 (95% CI 0.58−0.82), p<0.001 • OS HR=0.67 (95% CI 0.55−0.82), p<0.0001 favouring E-CMF • Independent prognostic factors were nodal status, tumour grade and size, ER status, vascular/lymphatic invasion; these did not significantly interact with effect of E-CMF • Adverse effects significantly higher with E-CMF but did not significantly affect QoL <u>2010 publication</u> • 21% were HER2 amplified, 10% TOP2A amplified, 11% TOP2A deleted, 23% Ch17CEP duplication, 61% high Ki-67 (>13%); • E-CMF significantly better for RFS (p=0.001−0.009) and OS for all categories (p=0.01−0.04)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								• HER2 amplification and TOP2A deletion were significant prognostic factors for RFS and OS • No significant interaction with anthracycline benefit for Ki-67, HER2, HER1−3, TOP2A • Ch17CEP duplication associated with significant improvement with anthracycline use • RFS: HR=0.92, (95% CI 0.72−1.18) normal vs HR=0.52 (95% CI 0.34−0.81) duplication, interaction p=0.04 • OS: HR=0.94 (95% CI 0.72−1.24) vs HR=0.57 (95% CI 0.36−0.92), interaction p=0.02
Earl, 2012[34]	NEAT, BR9601	See previous entry in table	2391					• Median follow-up 7.4 y, E-CMF vs CMF, 5−y results • RFS: 78% vs 71%, HR=0.75 (95% CI 0.65−0.86), p<0.0001 • OS: 84% vs 78%, HR=0.76 (95% CI 0.65−0.89), p=0.0007
Earl, 2008[35] Poole, 2006[33]	NEAT 1996−2001	E→ CMF vs classic CMF QoL and adverse effects data	2021	Early stage	31% NO 45% N1 24% N2+ 44% T1 49% T2 5% T3	48% premenopausal 9% perimenopausal 37% postmenopausal 49% ER+, 32% ER−, 19% unknown	QoL substudy offered to all pts until 500 accrued, used EORTC QLQ-C30 and QLQ-BR23, and Women's Health Questionnaire at baseline, mid-chemotherapy, end of chemotherapy, 12 and 24 mo after baseline	• E-CMF vs CMF: 28% improvement in RFS and 30% OS • E-CMF produced low common adverse effects criteria (CTC) scores, although higher than CMF for nausea, vomiting, alopecia, constipation, stomatitis, infection (all p<0.001) and fatigue (p=0.03) • QoL over 2 y was equivalent despite minimally worse adverse effects for E-CMF during treatment • Conclude E-CMF is significantly more effective with no serious long-term adverse effects or QoL detriment
Van Nes,	POCOB, EORTC	FEC preoperative vs FEC postoperative	698	Early stage, T1c−T3, T4b;	59% pN+ 51% cN+	42% ER+ 20% ER−	Pts ≥50 y assumed	Median follow-up of 10 y: no statistically significant difference between the two

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
2009[36]	10902 1991−1999			N0−1	14% cT1 58% cT2 27%c T3−4 37% pT0−1 42% pT2 11% pT3−4	37% unknown 7% aged ≤35 y 48% aged 35−50 y 45% aged >50 y	postmenopausal and received tamoxifen for 2 y; BCS +RT or modified radical mastectomy	treatment arms •OS: 66% postoperative, 64% preoperative, HR=1.09 (95% CI 0.83−1.42), p=0.54 •DFS: HR=1.12 (95% CI 0.90−1.39) p=0.30 •LRR: HR=1.16 (95% CI 0.77−1.74) •Preoperative chemotherapy was associated with an increase in BCT rates. BCT feasible due to tumour downsizing after preoperative chemotherapy was not correlated with higher LRR or worse OS compared with BCT which was feasible without downsizing of the tumour.
Canney 2012, 2014[10-12]; Velikova 2014[13] [abstracts only]	TACT2, CRUK/05/019 2005−2008	Accelerated epirubicin (aE) + pegfilgrastim vs E; then X vs classic CMF E-CMF is control	4371 female pts, 20 male pts	N+ or high risk N0 invasive early breast cancer			1 y trastuzumab if HER2+; 5 y endocrine therapy if HR+	•Median follow-up 61 mo, X vs CMF: •TTR events: 14.0% vs 14.4%, HR=0.98 (95% CI 0.84−1.15),p=0.79 •OS: HR=1.00 (95% CI 0.84−1.20) •DFS: HR=0.99 (95% CI 0.86−1.15) •Fewer serious adverse effects (except diarrhea and PPE) and better global QoL with X than CMF •Concluded X non-inferior efficacy but superior tolerability •Median follow-up of 49 mo, aE vs E • TTR: 3−y recurrence rates 91.0% vs 90.9%, 5−y recurrence rates 86.4% vs 85.2%; HR=0.96 •OS 94.4% vs 95.4% at 5 y (p=0.23) •After 4 cycles, more nausea, vomiting, appetite loss, constipation, systemic adverse effects and deterioration of functioning (global QoL, role function) with aE than E but these did not persist to 12 or 24 mo. •At end of 8 cycles, CMF had more adverse effects than X (fatigue, dyspnea, insomnia, constipation, systemic side-effects, deterioration of functioning) and these

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								(e.g., fatigue) often persisted to 24mo • Impact on menstruation assessed at 18 mo for premenopausal aged <50 y (N=1622): E→ X had lower risk of permanent loss of menstrual function than E→ CMF (28% vs 69%); aE vs E had more-short term amenorrhea but effect lost by 18 m
Budd, 2011, 2013[37,38] [abstracts]	SWOG S0221 2003−2012	AC vs ddAC, then second randomization to P(80 mg/m^2)q1w×12 vs P(175mg/m^2)q2w×6 **AC**=A(24 mg/m^2)q1w×15 + C(60mg/m^2)q1d + filgrastim **ddAC**=AC(60/600 mg/m^2) q2w×6 + pegfilgrastim	2716	N+ or high risk N0; operable				At first interim analysis after 2716 pts, a Cox model adjusted for paclitaxel arms had a HR=1.21 (95% CI 0.98−1.50, p=0.071) favouring ddAC; therefore, AC was stopped for futility. All subsequent pts received ddAC and then randomized to weekly or biweekly P
Lee, 2008[39]	2002−2005	Neoadjuvant TX→ surgery→ AC vs Neoadjuvant AC→ surgery→ TX	204	N+, Stage II/III	Stage II/III 77% T1−2, 23% T3−4 69% N1, 31% N2−3	61% HR+ 34% HER2+ 47% HER2− 18% unknown	All received RT; tamoxifen or anastrozole if HR+	At median follow-up of 37 mo, no significant difference in DFS by treatment groups (p=0.932). Compared with AC, TX increased pCR in primary tumours (21% vs 10%, p=0.024) and clinical response (84% vs 65%, p=0.003). Fewer pts developed recurrence who achieved pCR in lymph nodes HR=0.189 (95% CI 0.044−0.815), p=0.025 in the multivariate analysis. TX was associated with less nausea and vomiting, but more stomatitis, diarrhea, myalgia, and skin/nail changes than with AC
Burnell, 2010[40]	MA.21 2000−2005	CEF vs dd EC→ P vs AC→ P Filgrastim and epoetin permitted with CEF or AC→ P, required with EC→ P; Prespecified interim analysis for RFS after 261 events at median follow-up of 30.4 m	2104	N+ or high risk N0 (≥1cm plus one or more of: ER−, grade 3, or lymphovascular invasion); age ≤60 y	28% N0, 43% N1, 22% N2, 6% N3 35% T1 55% T2 9% T3 1% T4	Premenopausal or early postmenopausal (age <60 y); 41% ER+ 11% HER2+, 70% HER2−, 19% unknown	Stratified by number of positive nodes, type of surgery, ER status; BCS +RT or mastectomy (PMRT permitted); ER+	3−y adjusted RFS for CEF, EC→ P, AC→ P were 90.1%, 89.5%, 85% (p=0.001); pairwise comparison: AC→ P vs CEF: HR=1.49 (95% CI 1.12−1.99), p=0.005 AC→ P vs EC→ P: HR=1.68 (95% CI 1.25−2.27), p=0.0006 EC→ P vs CEF: HR=0.89 (95% CI 0.64−1.22), p=0.46

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
							received tamoxifen, AI allowed after Oct 2004; trastuzumab for 1 y for HER2+ was allowed after June 2005	Adverse effects: CEF, EC→ P compared with AC/P: febrile neutropenia: 22.3% CEF, 16.4% EC/P 4.8% AC/P (p=0.001); erythrocyte transfusion 23.8% CEF, 39.9% EC→ P, 1.6% AC/P (p<0.001); grade 3−4 cardiotoxicity higher in CEF (2.1%) vs 0.7% and 0.3% (p<0.001) AC→ P inferior for RFS but fewer adverse effects
Janni, 2012[41]; Schoenherr 2010[42] [abstract]	ADEBAR (only in abstract form)	Dose-intensive $FE_{120}C$ vs $E_{90}C$→ T FE_{120} C: F 500 mg/m^2 days 1+8 + E 60 mg/m^2 days 1+8 + C 75 mg/m^2 days 1−14, q4w×6 $E_{90}C$→T: E 90 mg/m^2 + C 600 mg/m^2 q21d×4→ T 100mg/m^2 q21d×4	1502	N2+				Median 49.5 mo observation Events: HR=0.877 (95% CI 0.722−1.065), p=0.38 OS: HR=0.996 (95% CI 0.783−1.267), p=0.969 Different adverse effects profiles: FEC had more hematological adverse effects, more infection (20% vs 10%), required more GCSF (61% vs 39%) and erythropoietin stimulation (20% vs 8.7%), p<0.0001 Myalgia and arthralgia occurred significantly more often in the EC→ T-arm (12.3 vs 1.4%, p<0.0001). Neurological symptoms and dermal adverse effects were found almost exclusively in the EC→ T arm (3.9% vs 0.3%, 4.2% vs 0.8% p=0.0001)
Earl, 2014[24]	Neo-tAnGo	Neoadjuvant: EC→ P vs P→ EC vs EC→ GP vs GP→ EC Effect of gemcitabine and role of sequence (EC→ P vs P→ EC) Stratified by ER status, tumour size (50 mm cut-off), nodal status (N0/N+), inflammatory/locally advanced (yes/no)	831	Early invasive, >2 cm; no previous chemo, RT, endocrine therapy T4 eligible	80% T2, 20% T3 50% N+	67% ER+ 51% PR+ 25% inflammatory or LABC; 57% premenopausal, 5% perimenopausal		Median follow-up 47 mo; first planned interim analysis found no significant difference in DFS or OS • DFS • EC→ P vs EC→ PG, HR=1.13 (95% CI 0.88−1.46), p=0.34; • P→ EC vs EC→ P HR=0.84 (95% CI 0.65−1.09), p=0.18 • OS • EC→ P vs EC→ PG HR=1.02 (95% CI 0.76−1.39), p=0.89; • P→ EC vs EC→ P HR=0.82

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								(95% CI 0.60−1.11), p=0.19 • pCR greater with P→ EC than EC→ P (20% vs 15%, p=0.03); G did not increase pCR • pCR was correlated with significant improvement in DFS (p<0.0001) and OS (p=0.0007)
Kerbrat, 2012[43] [abstract]	PACS 05 2002−2006	FEC-100 q3w×6 vs FEC-100q3w×4 F 500 mg/m^2, E 100 mg/m^2, C 500 mg/m^2	1515	High-risk N0. Operable, N0, >1 cm and another poor prognostic factor (T >2 cm, HR−, SBR grade II or III, aged <35 y)			HR+ pts received 5 y hormonal therapy; after Aug 2005 excluded HER2+ pts	Median follow-up 73 mo PFS: 12.0% vs 14.0% No difference in DFS, DDFS, local relapse, OS More grade III and IV neutropenia after 6 cycles

Abbreviations: AC, doxorubicin (Adriamycin) + cyclophosphamide; aE, accelerated epirubicin; AI, aromatase inhibitor; ALND, axillary lymph node dissection; BCS, breast-conserving surgery; BCT, breast-conserving therapy (BCS + RT); CEF, cyclophosphamide + epirubicin + fluorouracil; CEX, cyclophosphamide + epirubicin + capecitabine; CMF, cyclophosphamide + methotrexate + fluorouracil; dd, dose-dense; ddAC, dose-dense AC; DFS, disease-free survival rate; DDFS, distant disease-free survival rate; E, epirubicin; EC, epirubicin + cyclophosphamide; EFS, event-free survival rate; ER, estrogen receptor; FEC, fluorouracil + epirubicin + cyclophosphamide; G, gemcitabine; GCSF, granulocyte-colony stimulating factor; GnRH, gonadotropin-releasing hormone; HEC, high-dose EC; HER2, human epidermal growth factor receptor 2; HER2−E, HER-2 enriched; HR, hazard ratio; HR+, hormone receptor positive; HR−, hormone receptor negative; IDFS, invasive disease-free survival rate; LABC, locally advanced breast cancer; LRR, locoregional recurrence; N0, node-negative; N+, node-positive; OS, overall survival rate; P, paclitaxel; PG, paclitaxel + gemcitabine; pCR, pathologically complete response; PMRT, postmastectomy radiotherapy; pts, patients; PR, progesterone receptor; QoL, quality of life; RFS, recurrence-free survival rate; RT, radiation therapy (radiotherapy); T, docetaxel (Taxotere); TLI, thymidine labeling index; TX, docetaxel + capecitabine; X, capecitabine.

*HER2, ER/PR, lymph node, risk, menopausal status

Intrinsic Subtypes: luminal A=(ER+ and/or PR+) and not (HER2+ or Ki-67^{high}); luminal B=(ER+ and/or PR+) and either (HER2+ and/or Ki-67^{high}); HER2=HER2+ and ER−; triple negative (TN)=PR− and ER− and HER2−; basal=TN and either (EGFR+ or cytokeratins 5/6+)

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Supplemental Table 3. Taxanes: Paclitaxel and docetaxel.

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Taxane + anthracycline (sequential) vs same anthracycline regimen								
Rastogi, 2008[44]	NSABP B-27 1995−2000	See neoadjuvant section later in this table						
Mamounas, 2005[45]	NSABP B-28 1995−1998	AC vs AC→ P AC: A (60 mg/m^2) + C (600 mg/m^2) q3w×4 AC→ P: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ P (225 mg/m^2) q3w×4 • Before each P cycle, dexamethasone (20mg), diphenhydramine (50mg), and cimetidine (300mg) or ranitidine (50 mg) • All ER+ or PR+ pts or pts aged ≥50 y at time of surgery: tamoxifen (20mg/d) for 5 y beginning first day of AC cycle • Primary prophylaxis with GCSF not allowed, secondary prophylaxis mandated following a cycle complicated by prolonged neutropenia, febrile neutropenia, or grade 3−4 infection	3060	N+, cT1−3, cN0−1	70% N1 26% N2 4% N3 59% T1 32% 2.1−4 cm 8% ≥4 cm	66% ER+ 34% ER−/ borderline 61% PR+ 39% PR−/borderline	Tamoxifen for 5 y administered if age ≥50 y or HR+; RT after BCS, PMRT prohibited	5−y survival rates DFS: 76% AC→ P vs 72% AC, RR=0.83 (95% CI 0.72−0.95), p=0.006 OS: 85% for both groups, RR=0.93 (95% CI 0.78−1.12), p=0.46 Subgroup analysis on the effect of paclitaxel according to hormone receptor status and tamoxifen administration did not find statistically significant interaction Adverse effects with AC→ P were acceptable
Pusztai, 2009[46]	NSABP B-28	See previous entry in table[45] Tau protein expression	1924					No significant interaction between Tau expression and benefit from paclitaxel in total population or pts with ER+ or ER− cancer

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Vici, 2012[47]	GOIM 9902 1999−2005	EC vs T→ EC High-dose EC (E 120 mg/m^2, C 600 mg/m^2) in both arms EC: E (120 mg/m^2) + C (600 mg/m^2) q3w×4 T→ EC: T (100 mg/m^2) q3w×4→ E (120 mg/m^2) + C (600 mg/m^2) q3w×4 Primary prophylaxis with GCSF not allowed; administered in subsequent cycles if treatment delay due to low granulocyte/platelet count or G4 febrile neutropenia	750	pN+ (at least 5 nodes removed), operable, T1−3	94% N1 4% N2 1% N3 41% T1 53% T2 6% T3	46% premenopausal 77% HR+ 28% HER2+	Tamoxifen for 5 y if HR+, starting Jan 2003 post-menopausal pts administered anastrozole for 5 y; RT for BCS, PMRT if 4+ positive nodes	Median follow-up 64 mo: report 5−y survival rates, T→ EC vs EC DFS: 73.4% in both arms, HR=0.99 (95% CI 0.75−1.31), p=0.95 DFS: no treatment differences between subgroups (T1 vs T2−3, ER and hormone receptor status) OS: 90.7% T→ EC vs 89.5% EC, HR=0.84 (95% CI 0.54−1.31), p=0.45 Adverse effects more common but manageable with T→ EC: G3−4 neutropenia (65% vs 54%, p=0.007); hypersensitivity (5.2% vs 0.3%, p<0.0001), reversible cardiotoxicity (1.4% vs 0.3%, p=0.23), skin (1.6% vs 0%, p=0.03), diarrhea (3.3% vs 0.3%, p=0.006) Found no advantage of adding T to high-dose EC
Henderson, 2003[48]	CALGB 9344 INT 0148 1994−1999	AC (A: 60, 75, or 90 mg/m^2) vs AC (A: 60, 75, or 90 mg/m^2)→ P AC: C (600 mg/m^2) + A (either: 60 mg/m^2 on day 1 or 75 or 90 mg/m^2 on days 1 or 2) q3w×4 AC→ P: C (600 mg/m^2) + A (either: 60 mg/m^2 on day 1 or 75 or 90 mg/m^2 on days 1 or 2) q3w×4→ P (175 mg/m^2) q3w×4 Filgrastim (5µg/kg/d) + ciprofloxacin (750 mg 2×daily) administered routinely to pts receiving A 90 mg/m^2;	3121	Operable, N+	46% N1 42% N2 12% N3 35% T1 52% T2 13% T3	62% premenopausal 66% HR+ 59% ER+	Tamoxifen administered for 5 y to 94% of pts with HR+ cancer and 21% of pts with HR− cancer; RT for BCS, PMRT elective	Median follow-up 69 mo, 5−y survival rates, AC→ P vs AC DFS: 69%, 66%, 67% for increasing doses of A (no dose effect) DFS: 70% AC→ P vs 65% AC, p=0.0023 OS: 80% AC→ P vs 77% AC, HR=0.82 (95% CI 0.71−0.95), p=0.0064 Unplanned subset analysis: ER−: HR=0.72 (95% CI 0.59−0.86) ER+: HR=0.91 (95% CI 0.78−1.07) Without tamoxifen: HR=0.69 (95% CI 0.57−0.84) With tamoxifen: HR=0.92 (95% CI 0.79−1.08)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		only after an episode of febrile neutropenia for other pts						Additional adverse effects from adding P were generally modest P resulted in fewer hematological adverse effects (16% vs 62% granulocytopenia for lowest dose AC), less other adverse effects (nausea, vomiting, stomatitis, cardiotoxicity) Higher doxorubicin doses vs lower doses resulted in significantly more dose reductions and delays (p<0.001) and cardiotoxicity (p=0.0032)
Sartor, 2005[49]	CLGB 9344	See previous entry in table[48] Subgroups were records indicate patient received BCS +RT	169					5−y cumulative incidence of isolated LRR after BCS + RT: 3.7% AC→P vs 9.7% AC, p=0.04
Hayes, 2007[50]	CLGB 9344	See previous entry in table[48] Randomly selected tissue blocks from subset of 1500 female pts from study; analyzed 1322 by IHC for HER2	1322					No interaction observed between HER2+ and doxorubicin doses HER2+ associated with significant benefit from paclitaxel, interaction HR=0.59, p=0.01, regardless of ER status Paclitaxel did not benefit HER2− ER+ cancers
Berry, 2009[51] [abstract]	CLGB 9344	See previous entry in table[48] HER2 and ER status from tissue microarrays from 2039 pathology blocks from the study, including 957 that were part of previous HER2 study[50]; plus results of the previous study where samples not re-analyzed	2376					HER2 had significant interaction with P for RFS, p=0.001 RFS for P vs not P: HER2− ER− : HR=0.89 (95% CI 0.79−0.99), p=0.027, N=681 HER2− ER+ : HR=1.01 (95% CI 0.92−1.10), p=0.95, N=1342 HER2+ ER− : HR=0.73 (95% CI 0.59−0.89), p=0.0018, N=192 HER2+ ER+ : HR=0.77 (95% CI 0.65−0.92), N=277 Results were similar for OS (not reported)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								AC→ P in pts with N+ cancer improves outcome for HER2+ tumours and TN or double-negative tumours, but does not benefit ER+HER2− (which are majority of pts)
Lara, 2011[52]	CLGB 9344	See previous entry in table[48] From trial, evaluated 1887 patient specimens for p53 expression using IHC antibodies (mAbs 1801 and D07)	1877			P53 expression: 23% by mAbs 1801 and 27% by mAbs D07, 92% concordance		P53+ associated with worse OS with either antibody P53 staining with mAb 1801 had significantly worse RFS P53 not predictive of RFS or OS from either doxorubicin dose escalation or addition of paclitaxel
Cognetti, 2008[53] [abstract]	TAXIT 216 1998−2002	E→ T→ CMF vs E→ CMF E→ CMF: E (120 mg/m^2) q3w×4→ C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8, q4w×4 E→ T→ CMF: E (120 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4→ CMF	998	Early, N+				Median follow-up 62 mo, report 5−y survival rates, E→ T→ CMF vs E→ CM DFS: 74% vs 68%, HR=0.82 (95% CI 0.64−1.03), p=0.13 RFS: 76% vs 69%, HR=0.75 (95% CI 0.59−0.96), p=0.039 OS: 90% vs 85%, HR=0.67 (95% CI 0.48−0.94), p=0.017
Taxane + anthracycline (sequential) vs more non-taxane (anthracycline) regimen								
Francis, 2008[54]	BIG 02−98 1998−2001	A→ CMF (sequential control) vs AC→ CMF (concurrent control) vs A→ T→ CMF (sequential docetaxel) vs AT→ CMF (concurrent docetaxel) *In all arms, if oral C not tolerated, IV C (600 mg/m^2) used A→ CMF: A (75 mg/m^2) q3w×4→ C (100 mg/m^2) + M (40 mg/m^2) + F (600	2887	N+ (at least 8 nodes dissected), T1−3	54% N1 46% N2−3 92% pT1−2 7% pT3	54% premenopausal 76% HR+, 24% HR−	Tamoxifen administered for 5 y if HR+, from 2004 on allowed sequential AIs in post-menopausal pts and ovarian suppression in	Analysis after 5 y DFS: 73% A, 72% AC, 78% A→ T, 74% AT DFS: T vs control: HR=0.86 (95% CI 0.74−1.00), p=0.051 DFS: sequential T vs control: HR=0.79 (95% CI 0.64−0.98), p=0.035 DFS: concurrent T vs control: HR=0.93 (95% CI 0.75−1.14), p=0.48 DFS: sequential T vs concurrent T: HR=0.83 (95% CI 0.69−1.00) [survival rate

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		mg/m^2) days 1&8 q4w×3 AC→ CMF: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ C (100 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×3 A→ T→ CMF: A (75 mg/m^2) q3w×3→ T (100 mg/m^2) q3w×3→ C (100 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×3 AT→ CMF: A (50 mg/m^2) + T (75 mg/m^2) q3w×4→ C (100 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×3 Unbalanced randomization, ratio: 1:1:2:2 Ciprofloxacin administered during AT cycles; primary GCSF prophylaxis not permitted, but recommended with subsequent doses in cases of previous febrile neutropenia, grade 3−4 infection, delay >7 d due to neutropenia					pre-menopausal; RT after BCS, PMRT according to institutional guidelines	better with sequential T] No heterogeneity of effect with regard to efficacy of T found in subgroups according to age, lymph node status or hormone status Too early to report OS Febrile neutropenia, severe asthenia, myalgias, diarrhea, skin adverse effects, andneurosensory adverse effects more common with T than in controls
Oakman 2013[55]	BIG 02−98	See previous entry in table[54]	2887					Median follow-up 93.4 mo • DFS (T vs no T): HR=0.91 (95% CI 0.80−1.05), p=0.187 • DFS (sequential T vs sequential control): HR=0.81 (95% CI 0.67−0.99), p=0.036 • DFS (sequential A→ T vs concurrent AT):

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								HR=0.84 (95% CI 0.72−0.99), p=0.035 • OS (sequential A→ T vs concurrent AT): HR=0.79 (95% CI 0.65−0.98), p=0.028 Better OS and DFS with A→ T compared with concurrent AT
Fernandez-Cuesta, 2012[56]	BIG 02−98 1998−2001	See previous entry in table[54] Retrospective analysis of TP53 mutations for 18% of pts; classified as wild type (no TP53 variations or variations which do not modify p53 protein) or mutant	520			17% mutants		P53 status had no significant predictive value for response to docetaxel P53 truncating mutations were uncommon (3.6%) but associated with poor prognosis
Martin, 2013[57]	GEICAM/ 2003−02 2003−2008	FAC→ P vs FAC FAC (500/50/500 mg/m^2)q3w×4→ P (100 mg/m^2)q1w×8 vs FAC (500/50/500 mg/m^2) q3w×6	1925	T1−3, N0 and at least one high-risk factor (age <35 y, T2+, HR−, histological grade 2−3)	58% T1 40% T2	50% premenopausal	HER2+ pts excluded after 2005 (792 pts already recruited); 73% HR+, 9.4% HER2+	Median follow-up 63.3 mo • 5−y DFS: 93% vs 90.3%, HR=0.73 (95% CI 0.54−0.99), p=0.04 • OS: 97% vs 96%, HR=0.79 (95% CI 0.49−1.26), p=0.31 • 1 vs 7 deaths from cardiovascular disease Grade 3/4 adverse events: neutropenia 22% vs 25% (p=0.07), febrile neutropenia 2.7% vs 3.6% (p=0.22), fatigue 7.9% vs 3.4% (p<0.01), sensory neuropathy 5.5% vs 0% (p<0.01), myalgia 1.5% vs 0.2% (p<0.01), thrombosis/embolism 1.1% vs 0.1% (p<0.01)
Delbaldo, 2014[58]	AERO-B2000 2000−2002	FEC_{100}→ P vs FEC_{100} FEC (500/100/500 mg/m^2)q3w**×4→** P(175 mg/m^2)q3w×4 vs FEC(500/100/500 mg/m^2)q3w**×6**	837	N+	Mean 4.3 positive nodes; 43% T1, 46% T2	73% ER+, 62% PR+	Planned 1000 pts, closed early due to slow accrual; RT according to standard practice of each centre;	Median follow-up 108 mo DFS HR=0.99 (95% CI 0.77−1.26), p=0.91 OS HR=0.85 (95% CI 0.62−1.15), p=0.29 5−y DFS 78.4% FEC→ P vs 78.5% FEC 9−y DFS 62.5% FEC→ P vs 62.9% FEC 5−y OS 88.6% FEC→ P vs 86.1% FEC 9−y OS 77% FEC→ P vs 73.9% FEC

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							HR+ administered 5 y tamoxifen or AI	Overall grade 3−4 adverse effects similar (58% FEC→ P vs 63% FEC, p=0.16); neuropathy 2.9% vs 0.2%, p=0.002; myalgia 3.2% vs 0.5%, p=0.003; cardiac 0.3% vs 0.5% (NS) May be lack of power to detect small benefits
Martín, 2008[59]	GEICAM 9906 1999−2002	FEC×6 vs FEC×4→ P (eight 1− w courses) FEC: F (600 mg/m^2) + E (90 mg/m^2) + C (600 mg/m^2) q3w×6 FEC→ P: F (600 mg/m^2) + E (90 mg/m^2) + C (600 mg/m^2) q3w×4→ P after three weeks no treatment P(100 mg/m^2) q1w×8 Primary GCSF prophylaxis not permitted, but mandatory for pts with at least one episode of febrile neutropenia or infection	1246	N+ (at least 6 nodes isolated), T1−3	62% N1, 38% N2−3 43% T1 52% T2 36% T3	54% premenopausal 82% HR+ (investigator report), 66% HR+ (central) 20% HER2+	Tamoxifen if ER+ or PR+, AIs allowed in menopausal pts after Sept 2005; RT after BCS, PMRT according to institutional guidelines (mostly T3 or N2−3)	At 5 y, FEC→ P vs FEC DFS 78.5% in FEC→ P, 72.1% in FEC, p=0.006 OS: 22% reduction, HR=0.78 (95% CI 0.57−1.06), p=0.110 Risk of relapse: 23% reduction, HR=0.77 (95% CI 0.62−0.95), p=0.022 No significant interaction between HER2 or hormone receptor status and paclitaxel treatment
Martín, 2010[60]	GEICAM 9906	See Martín, 2008[59] Molecular predictors of efficacy					928 (74.5%) samples had evaluation of molecular subtype	At 7−y follow-up, FEC→ P vs FEC: Benefit with FEC→P is now statistically significant DFS 75% vs 68%, HR=0.75 (95% CI 0.61−0.93), p=0.007 OS: 84% vs 79%, HR=0.74 (95% CI 0.56−0.96), p=0.026 Benefit small in absolute terms, attempted to find subgroups that benefit more Superiority of FEC→ P greater in HR−/HER2− (TN), particularly in subset with

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								basal phenotype (TN and either EGFR+ or cytokeratins 5/6+) and for luminal A (p=0.034) TN: FEC→ P reduced likelihood of relapse by 47% and yielded and absolute benefit of 18% DFS compared with FEC (74% vs 56%), p=0.015 Basal (N=79): DFS 83% FEC→ P vs 57% FEC, p=0.018 HR=0.33 (95% CI 0.12−0.87),p=0.024
Fountzilas, 2008[61]	HE 10/00 2000−2005	Group A: Sequential E→ P→ CMF vs Group B: Concurrent E+P→ CMF E→ P→ CMF: E (110 mg/m^2) q2w×3→ P (250 mg/m^2) q2w×3→ C (840 mg/m^2) + M (57 mg/m^2) + F (840 mg/m^2) q2w×3 E+P→ CMF: E (83 mg/m^2) + P (187 mg/m^2) q3w×4→ C (840 mg/m^2) + M (57 mg/m^2) + F (840 mg/m^2) q2w×3 Cumulative dose almost identical in both groups Prophylactic GCSF for dose-dense treatments	1121	T1−4, N1−2	48% N1 52% N2+ (median 3−4 positive nodes) 32% T1 57% T2 11% T3+	69% ER+, 61% PR+, 73% HR+ 46% premenopausal 33% HER2+	5 y tamoxifen for HR+, 2 y ovarian suppression if premenopausal, switched in 2004 to 2−3 y tamoxifen + 2−3 y exemestane; RT for BCS, PMRT if N2+and/or T3+	Group A (dose-dense) had more thrombocytopenia (1.1% vs 0%, p=0.03), severe sensory neuropathy (9.5% vs 2.1%, p<0.001), hypersensitivity (5.2% vs 1.4%, p<0.001), severe arthralgias/myalgias (3% vs 0.8%, p=0.01), and discontinuation of chemotherapy (6.5% vs 3%, p=0.003) Conclude rates of severe adverse effects low, but significantly increased with dose-dense sequential regimen (Group A)
Gogas, 2012[62]	HE 10/00 2000−2005	See Fountzilas 2008[61]						Median follow-up 76 mo; 5−y survival rates, Group A (sequential) vs B (concurrent) DFS: 74% and 74%, p=0.78 OS: 86% and 85%, p=0.45 Subgroup by disease subtypes: no significant differences in response by hormone receptor status, HER2 status, TN

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								Conclude no DFS or OS benefit Group A vs B
Burnell, 2010[40]	MA.21 2000−2005	CEF vs dd EC→ P vs AC→ P CEF: C (75 mg/m^2; days 1−14) + E (60 mg/m^2; days 1&8) + F (500 mg/m^2; days 1&8) q4w×6 EC→ P: E (120 mg/m^2) + C (830 mg/m^2) q2w×6→ P (175 mg/m^2) q3w×4 AC→ P: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4 Filgrastim and epoetin permitted with CEF or AC→ P, required with EC→ P; Prespecified interim analysis for RFS after 261 events at median follow-up of 30.4 mo	2104	N+ or high risk N0 (≥1cm plus one or more of: ER−, grade 3, or LVI); age ≤60 y	28% N0, 43% N1, 22% N2, 6% N3 34% T1 55% T2 9% T3 1% T4	Premenopausal or early post-menopausal (age <60 y); 41% ER+ 11% HER2+, 70% HER2−, 19% unknown	Stratified by number of positive nodes, type of surgery, ER status; BCS +RT or mastectomy (PMRT permitted); ER+ received tamoxifen, AI allowed after Oct 2004; trastuzumab for 1 y for HER2+ was allowed after June 2005	3−y adjusted RFS for CEF, EC/P, AC/P were 90.1%, 89.5%, 85% (p=0.001); pairwise comparison: • AC→ P vs CEF: HR=1.49 (1.12−1.99), p=0.005 • AC→ P vs EC/P HR=1.68 (1.25−2.27), p=0.0006 • EC→ P vs CEF: HR=0.89 (95% CI 0.64−1.22), p=0.46 Adverse effects: febrile neutropenia was 22.3% and 16.4% in CEF and EC→ P pts compared with 4.8% in AC→ P (p=0.001); erythrocyte transfusion 23.8%, 39.9%, 1.6% (p<0.001); grade 3−4 cardiotoxicity higher in CEF (2.1%) vs 0.7% and 0.3% (p<0.001); full adverse effects comparison listed AC→ P inferior for RFS but fewer adverse effects [see CALGB 9741 for higher-dose AC→ P[63]]
Polyzos, 2010[64]	HORG 1995−2004	T→ EC vs FEC T→ EC: T (100 mg/m^2)→ E (75 mg/m^2) + C (700 mg/m^2) q3w×4 FEC: E (75 mg/m^2) + C (700 mg/m^2) + F (700 mg/m^2) q3w×6 Epirubicin dose 75 mg/m^2 was lower	756	N+, ALND with at least 10 nodes removed, early, Stage II-IIIA	35% N1, 45% N2, 21%N3 53% T1, 40% T2, 5% T3, 3% unknown	71% ER+ and/or PR+ 20% ER−PR− 10% unknown 38% premenopausal	60%-70% HR+ and subsequently received adjuvant hormonal treatment; RT for all BCS, PMRT at	Median follow-up of 5 y Relapse: 28% T→ EC vs 33% FEC, p=0.181 DFS 72.6% (63.8−81.3) and 67.2% (58.0−76.4%), p=0.041; No difference in OS rates (83.8% vs 81.4%, p=0.533) T→ EC had increase neutropenia requiring GCSF (90.5% vs 74.1%, p=0.0001)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		than used in other studies; prophylactic GCSF not permitted, but allowed in subsequent courses if febrile neutropenia or grade 3−4 neutropenia or >7 d delay because of neutropenia					physician discretion	T→ EC had higher significantly more stomatitis, diarrhea, hypersensitivity reactions, nail disorders, neurotoxicities Conclude: improved DFS in pts with N+ cancer at expense of increased but manageable myelotoxicity
Joensuu, 2009[65]	FinHer 2000−2003	T→ FEC vs vinorelbine→ FEC T→ FEC: T (100 mg/m^2) q3w×3→ F (600 mg/m^2) + E (60 mg/m^2) + C (600 mg/m^2) q3w×3 Vinorelbine→ FEC: Vinorelbine (25 mg/m^2; days 1,8,15) q3w×3→ F (600 mg/m^2) + E (60 mg/m^2) + C (600 mg/m^2) q3w×3 Further randomization to receive trastuzumab if HER2+ (N=232, 2+ or 3+ on scale of 0−3+ by IHC, and 6+ gene copies) Prophylactic GCSF not recommended unless 1+ episodes of febrile neutropenia or severe infection Dose of T reduced from 100 to 80 mg/m^2 in Feb 2002 due to neutropenic fevers	1010	N+ or high risk N0 (>2 cm and PR−)	56% >2 cm 11% N0 61% N1 28% N2+	72% ER+ 23% HER2+	Tamoxifen for 5 y if HR+, amended Dec 2005 to allow switching to AI for post-menopausal pts after 2−3 y and to allow administration of AI for addition 2−3 y after completion of 5 y tamoxifen; RT according to each institutions guideline	5−y survival rates calculated OS=90.7% for entire series T vs vinorelbine, HR=0.70 (95% CI 0.46−1.05), p=0.086 DDFS rate (pts with only local recurrence were censored): T vs vinorelbine: HR=0.66 (95% CI 0.49−0.91), p=0.010 Subgroup HER2+: Trastuzumab better than without: HR=0.65 (95% CI 0.38−1.12), p=0.12; adjusted for nodal metastases HR=0.57, p=0.047 T + trastuzumab better than T, HR=0.32 (95% CI 0.12−0.89), p=0.029 T + trastuzumab better than vinorelbine + trastuzumab, HR=0.31 (95% CI 0.11−0.83), p=0.020 Vinorelbine ± trastuzumab HR=0.92 (95% CI 0.47−1.83), p=0.82 Median left ventricular ejection fraction of trastuzumab-treated pts remained unaltered during 5−y follow-up HER2− subgroup DDFS: 88.2% T vs 83.5% vinorelbine, HR=0.69 (95% CI 0.47−1.01), p=0.058 Docetaxel more favourable than

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								vinorelbine overall, and subsets N0, N+,
Nitz, 2009[66] [abstract]	EC-Doc WSG/AGO AM02 2000−2005	EC→ T vs control (FEC, N=828 or CMF, N=175) EC→ T: E (90 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 FEC: F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×6 CMF: C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) q4w×6	2012	N1, intermediate risk	Median 2.0 cm	78% HR+		Median follow-up 41 mo, estimated 5−y survival rates EFS: 91% vs 86%, p=0.005 (better in EC→ T arm) OS: 95% vs 90%, p=0.004 (better in EC→ T arm) EC→ T vs FEC: EFS 91% vs 85%, HR=0.58, p=0.004 EC→ T vs FEC: OS 95% vs 91%, p=0.03 HR+ subgroup, HR=0.51 in favour of EC→T, p=0.007 Conclude EC→ T is superior for EFS and OS over FEC
Huober, 2010[67] Nitz, 2011[68] Gluz, 2011[69] [abstracts]	EC-Doc	See previous entry in table	2012 (772 for protein analysis)				20% HER2+ ≈25 % Topo-II aberration (deletion or amplifica-tion) 49% HER2+ and 14% HER2− tumours had Topo-II aberration 65% TIMP-1	Median follow-up 64 mo: report 5−y survival rates DFS 90% EC→ T vs 80% FEC, p=0.006 OS: 95% EC→ T vs 92% FEC, p=0.022 DFS highest in luminal A (97%), lowest in TN basal-like (72%) Significant benefit of EC→ T vs FEC for DFS in pts with luminal B cancer: HR=0.41 (95% CI 0.22−0.77), p=0.004 In multivariate model, EC→ T vs FEC, HR=0.44 (95% CI 0.26−0.76), p=0.003 EC→ T better than FEC in HR− non-basal like, HR=0.385 (95% CI 0.14−1.07), p=0.057 Prospective WSG Plan B trial to

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								validate these results Ki-67 cut-off of 20% was significant regarding interaction with therapy (HR=0.467, p=0.02) DFS for subgroups, EC→ T vs FEC HER2: HR=0.29 (95% CI 0.12−0.7) p=0.006 HER2− : EC→ T vs FEC, not significant, p=0.18 Topo-II aberration: HR=0.28 (95% CI 0.11−0.69), p=0.006 Topo-II normal, not significant, p=0.16 TIMP-1 immunoreactive: HR=0.57, p=0.025 TIMP-1 negative, not significant, p=0.14 In multivariate model, only high Ki-67 had significant therapy interaction
Taxane + anthracycline (sequential) vs doubled non-taxane (anthracycline) regimen								
Ellis, 2009[70]	TACT CRUK01/001 ISRCTN79718493 2001−2003	FEC→ T vs control (either FEC or E→ CMF) FEC→ T: F (600 mg/m^2) + E (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 FEC: F (600 mg/m^2) + E (60 mg/m^2) + C (600 mg/m^2) q3w×8 E→ CMF: E (100 mg/m^2) q3w×4→ C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) q4w×4	4162	pT1−3a, pN0−1 Early, N+ or high risk N0 (grade 3, HR−, or lympho-vascular invasion)	34% T1 56% T2 9% T3 20% N0 44% N1 36% N2+	69% ER+ 31% ER− 20% HER2+ 65% HER2− 14% unknown	Tamoxifen for 5 y if HR+, from 2005 allowed AIs as an alternative; pts with HER2+ allowed to enter trials assessing trastuzumab; RT after BCS, PMRT	Median follow-up 62 mo, report survival rates at 5 y DFS: 75.6% vs 74.3 %, HR=0.95 (95% CI 0.85−1.08), p=0.44 OS: 82.5% vs 83%, HR=0.99 (95% CI 0.86−1.14), p=0.91 No difference due to choice of control regimen No strong evidence for differential effect by ER status or HER2 status Exploratory analysis consistent with improvement with taxane for ER− HER2+ subgroup, DFS HR=0.78 (95% CI 0.55−1.09),

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		GCSF used according to local practice					according to local guidelines	DFS for pts with N+ cancer HR=0.70 (95% CI 0.49−1.00) Acute grade 3 or 4 adverse events significantly greater in experimental group than in control group (p<0.0001), most frequent was neutropenia, leucopenia, lethargy; late adverse effects also more frequent with FEC→ T In QoL substudy there was significantly greater impairment in experimental group for physical, role, emotional and social functioning, pain, fatigue, global QoL, but less nausea and vomiting; returned to close to baseline levels over 24 mo Conclude: did not show any overall gain from addition of T to standard anthracycline therapy
Roche, 2006[71]	PACS 01 1997−2000	FEC vs FEC→ T FEC: F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×6 FEC→ T: F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×3→ T (100 mg/m^2) q3w×3 Primary prophylaxis with GCSF prohibited; administered for subsequent cycles of FEC in case of low granulocyte/platelet count or febrile neutropenia	1999	Operable, N+ (based on at least 5 nodes removed), Stage <T4a	62% N1 38% N2+ 37% T1 55% T2 8% T3	61% premenopausal 79% HR+, 21% HR− 74% ER+, 65% PR+	Tamoxifen for 5 y if HR+ and post-menopausal (optional for pre-menopausal until Dec 1998, after which it was required), some centres also gave for HR− RT after BCS, PMRT to	Median follow-up 60 mo, report 5−y survival rates DFS: 78.4% FEC→ T vs 73.2% FEC, HR=0.80 (95% CI 0.67−0.96), p=0.012 OS: 90.7% FEC→ T vs 86.7% FEC, HR=0.73 (95% CI 0.56−0.94), p=0.017 In subgroup analysis for DFS, FEC→ T was better or equivalent in all groups; there was significant benefit of FEC→ T for female pts aged ≥50 y or postmenopausal, but not premenopausal or aged <50 y Grade 3−4 neutropenia, need for hematopoietic growth factor, incidence of nausea/vomiting higher with FEC Febrile neutropenia (fourth cycle), stomatitis, edema, nail disorders higher with

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							chest wall, supra-clavicular area, internal mammary chain recommended following mastectomy but irradiation of the axilla prohibited	FEC→ T Fewer cardiac events after FEC→ T due to lower anthracycline cumulative dose
Coudert, 2009[72] [abstract] 2012[73]	PACS 01	See previous entry in table[71]						Update at median follow-up of 92.8 mo, report 8−y survival rates DFS: 70.2% FEC→ T vs 65.8% FEC, HR=0.85 (95% CI 0.73−0.99), p=0.036 OS: 83.2% FEC→ T vs 78.0% FEC, HR=0.75 (95% CI 0.62−0.92), p=0.007 Cardiac events 0.4% FEC→ T vs 2.1% FEC Confirms previous 5−y results
Penault-Llorca, 2009[74]	PACS 01	See previous entry in table[71] Measured ER, PR, Ki-67, HER2 by IHC in 55% of original samples (N=1190), and selected those ER+ for further analysis	798	ER+ subset		21% Ki-67 >20% 9% HER2+ 62% PR+ >10%		ER+ tumours (this study), median follow-up 58.7 mo DFS, 5 y: 82% FEC→ T vs 77% FEC, p=0.11 Relapse, FEC→ T vs FEC: All: HR=0.82 (060−1.12), p=0.22 Ki-67+ HR=0.51 (95% CI 0.26−1.01) Ki-67− HR=1.03 (95% CI 0.69−1.55) Hazard ratio for interaction with T HR=0.53 (95% CI 0.24−1.16), p=0.11 No trend for interaction with T

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								observed for HER2 or PR status
Jacquemier 2011[75]	PACS 01	See previous entry in table[71] Prepared tissue microarray for 1099 of the cases that had IHC[74], and evaluated expression of ER, PR, Ki-67, HER2 and 30 additional proteins	1099				Defined molecular subtypes: luminal A (HR+, HER2−, Ki-67−), luminal B (HR+, HER2−, Ki-67+), HER2 over-expressing TN (HR− HER2−)	In multivariate analysis, PR− and Ki-67+ remained associated with shorter DFS Interaction of protein expression and FEC→ T only significant for Ki-67, p=0.012 Ki-67+ HR=0.51 (95% CI 0.33−0.79), p=0.003 Ki-67− HR=1.10 (95% CI 0.75−1.61), p=0.612 Molecular subtypes analyzed for docetaxel benefit on risk of relapse: Luminal B: 53% reduction, HR=0.47 (95% CI 0.22−1.01), p=0.05 HER2 overexpressing: 34% reduction, HR=0.66 (95% CI 0.37−1.19), p=0.14 TN: 12% reduction, HR=0.88 (95% CI 0.49−1.57), p=0.67 Luminal A: 16% higher with T, HR=1.16 (95% CI 0.73−1.84), p=0.52 Interaction between benefit of T and each subtype was significant for luminal B (p=0.047), borderline for HER2 overexpressing (p=0.14) and not significant for TN (p=0.46) Added value of molecular subtype compared with Ki-67 alone did not show any significant added predictive value
Ladoire, 2012[76]	PACS 01	See previous entry in table[71] Assessed FOXP3 status in subgroup of 1097 pts by IHC	1097				37% FOXP3 expressed	Median follow-up 96 mo, FEC→ T vs FEC OS shorter in pts with FOXP3– For FOXP3–, OS shorter with FEC than FEC→ T For FOXP3+, no difference between FEC and FEC→ T

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								Interaction between FOXP3 and treatment arm was not significant; however, the statistical power of the interaction test was 13%
Sakr, 2013[77]	Mansoura University 2006−2010	FEC×3→ T×3 vs FEC×6 FEC (500/100/500mg/m^2) q3w×3→ T(100mg/m^2)q3w×3 vs FEC (500/100/500mg/m^2) q3w×6	657	Had surgery + AD with clear margins, high risk (T3−4 and/or N+)	34% T1, 51% T2, 7% T3 64% N1 36% N2+	79% HR+ 60% pre-menopausal	Almost all received RT, 78% received tamoxifen	Median 61 mo from randomization • 5−y DFS 74% FEC vs 78% FEC→ T • Multivariate analysis found 17% reduction in relative risk of relapse with FEC→ T (p=0.034); difference found in N2+ subgroup (p=0.042) but not N1subgroup; benefit of FEC→ T in female pts aged ≤50 y (p=0.03) but not aged >50 y (p=0.65) Fewer cardiac events with FEC→ T (0.3% vs 1.8%, p=0.02), less nausea-vomiting (11.2% vs 19%, p=0.001), more edema (3.6% vs 0.3%, p=0.001), and nail disorders (5.1% vs 0.9%, p=0.001)
Coombes, 2011[78]	DEVA 1997−2005	E vs E→ T E: E (50 mg/m^2; days 1&8) q4w×6 E→ T: E (50 mg/m^2; days 1&8) q4w×3→ T (100 mg/m^2; day 1) q3w×3 + dexamethasone 8mg orally 2×daily for 3 d each cycle Optional second random assignment of timing of tamoxifen (concurrently with chemotherapy or sequentially) in some centres, to be reported separately Prophylactic GCSF recommended in	803	Post-menopausal, N+, early	0.5% N0 66% N1 32% N2 1% unknown 44% T1 49% T2 6% T3	78% HR+ 19% HR− 3% unknown	Tamoxifen received by all pts, amended in 2001 to be omitted if HR− and in 2007 to allow AIs	Median follow-up 64.7 mo, report 5−y survival rates for E→ T vs E DFS: 79.5% vs 72.7%, HR=0.68 (95% CI 0.52−0.91), p=0.008 OS: 88.9% vs 81.8%, HR=0.66 (95% CI 0.46−0.94), p=0.02 E→ T associated with greater adverse effects but no difference in QoL Subgroup analysis found consistency with overall effect T gave higher level of grade 3−4 adverse effects: febrile neutropenia (p<0.001), neutropenia (p<0.001), skin disorders (p=0.002), stomatitis(p=0.009), diarrhea (p=0.01), and myalgia/arthralgia (p=0.04); also higher level of neurological disorders of any grade and more

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		case of febrile neutropenia						persistent effects: peripheral neuropathy, edema, and nail abnormality No significant differences in overall QoL Overall, substitution of T for E for last 3 cycles improved DFS and OS but more adverse effects
Burnell, 2010[40]	MA.21 2000−2005	CEF vs dose-dense EC→ P vs AC→ P CEF: C (75 mg/m^2; days 1−14) + E (60 mg/m^2; days 1&8) + F (500 mg/m^2; days 1&8) q4w×6 EC→ P: E (120 mg/m^2) + C (830 mg/m^2) q2w×6→ P (175 mg/m^2) q3w×4 AC→ P: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4 Filgrastim and epoetin permitted with CEF or AC→ P, required with EC→ P; Prespecified interim analysis for RFS after 261 events at median follow-up of 30.4 m	2104	N+ or high-risk N0 (≥1cm plus one or more of: ER−, grade 3, or lymphovas-cular invasion); age ≤60 y	28% N0, 43% N1, 22% N2, 6% N3 34% T1 55% T2 9% T3 1% T4	Premenopausal or early post-menopausal (<60 y old); 41% ER+ 11% HER2+, 70% HER2−, 19% unknown	Stratified by number of positive nodes, type of surgery, ER status; BCS +RT or mastectomy (PMRT permitted); ER+ received tamoxifen, AI allowed after Oct 2004; trastuzumab for 1 y for HER2+ was allowed after June 2005	3−y adjusted RFS for CEF, EC/P, AC/P were 90.1%, 89.5%, 85% (p=0.001); pairwise comparison: • AC→ P vs CEF: HR=1.49 (1.12−1.99), p=0.005 • AC→ P vs EC→ P HR=1.68 (1.25−2.27), p=0.0006 • EC→ P vs CEF: HR=0.89 (95% CI 0.64−1.22), p=0.46 Adverse effects: febrile neutropenia was 22.3% and 16.4% in CEF and EC→ P pts compared with 4.8% in AC→ P (p=0.001); erythrocyte transfusion 23.8%, 39.9%, 1.6% (p<0.001); grade 3−4 cardiotoxicity higher in CEF (2.1%) vs 0.7% and 0.3% (p<0.001); full adverse effects comparison listed AC→ P inferior for RFS but fewer adverse effects [see CALGB 9741 for higher-dose AC→ P[63]]
Janni, 2012[41] Schoenherr,	ADEBAR 2001−2005	$E_{90}C$→ T vs $FE_{120}C$ (dose-intensive anthracycline) EC→ T: E (90 mg/m^2) + C (600	1502	N2+			Anti biotics administered in 10% ECT	At median follow-up 49.5 mo, **FEC vs EC→ T**: Recurrence: 166 vs 193 events, HR=0.877 (95% CI 0.722−1.065), p=0.382

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2010[42] [abstracts]		mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 FEC: F (500 mg/m^2; days 1&8) + E (60 mg/m^2; days 1&8) + C (75 mg/m^2; days 1&14) q4w×6					vs 20% FEC GC SF administered in 39% ECT vs 61% FEC Eryt hro-poietin administered in 9% ECT vs 20% FEC	OS: 131 vs 134 deaths, HR=0.996 (95% CI 0.783−1.267), p=0.969 Subgroup analysis found no significant difference between the two arms Treatment stopped early due to adverse effects in 3.7% EC→ T and 8% FEC (p=0.0009) Neutropenia grade 3−4 and febrile neutropenia similar in both groups Hematological adverse effects significantly higher in FEC arm Non-hematological adverse effects grade 3−4 seldom found in either arm EC→ T had higher myalgia and arthralgia (12.3 vs 1.4%, p=0.0001), neurological symptoms (3.9% vs 0.3%), dermal adverse effects (4.2% vs 0.8%) Conclude EC→ T is well tolerated feasible alternative to $FE_{120}C$
Albert, 2011[79]	1994−1998	P→ FAC vs FAC P→ FAC: P (250 mg/m^2) q3w×4→ F (500 mg/m^2; days 1&4) + A (50 mg/m^2; days 1−3) + C (500 mg/m^2; day 1) q3w or q4w×4 FAC: F (500 mg/m^2; days 1&4) + A (50 mg/m^2; days 1−3) + C (500 mg/m^2; day 1) q3w or q4w×8	511	T1−3, N0−1	4% Stage 0, 17% Stage I, 43% Stage IIA, 30% Stage IIB, 5% Stage IIIA, 1% Stage IIB 31% N0, 38% N1, 28% N2+, 3% unknown	54% premenopausal 3% peri-menopausal 32% post-menopausal 11% surgical; 59% ER+, 37% ER−, 4% unknown; 58% PR+, 37% PR−, 6% unknown	Tamoxifen for 5 y if aged ≥ 50 y and ER+; RT after BCS, PMRT at discretion of physician	Median follow-up 124 mo, no difference in locoregional recurrence or death rates: OS at 10 y: 78.4% in FAC arm vs 81.7% in P→ FAC, p=0.930 No difference in OS between subgroups (BCT, mastectomy, PMRT, N+)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
Taxane + anthracycline (concurrent) vs more non-taxane (anthracycline)								
Martín, 2005[80]	BCIRG 001 1997−1999	TAC vs FAC TAC: A (50 mg/m^2) + C (500 mg/m^2) + T (75 mg/m^2) q3w×6 FAC: A (50 mg/m^2) + F (500 mg/m^2) + C (500 mg/m^2) q3w×6 Primary prophylaxis with GCSF not allowed; pts with one episode of febrile neutropenia or infection were administered GCSF in subsequent cycles	1491	N+, T1−3; exclude advanced disease (T4, N2−3, M1)	62% N1 38% N2+ 41% T1 52% T2 7% T3	55% premenopausal 76% HR+ 22% HER2+, 15% unknown	Tamoxifen for 5 y administered if HR+; RT after BCS, PMRT according to institution guidelines	Median follow-up 55 mo; estimated 5−y survival rates DFS: 75% TAC vs 68% FAC, p=0.001 OS: 87% TAC vs 81% FAC, p=0.008 Grade 3 or 4 neutropenia 65.5% vs 49.3 % (p<0.001), febrile neutropenia 24.7% vs 2.5% (p<0.001), infections 3.9% vs 2.2% (p=0.05)
Mackey, 2013[81]	BCIRG 001	See previous entry in table	1491					Median follow-up 124 mo • DFS: 62% TAC vs 55% FAC, HR=0.80 (95% CI 0.68−0.93), p=0.0043 • OS (10 y): 76% TAC vs 69% FAC, HR=0.74 (95% CI 0.61−0.90), p=0.0020 • TAC improved DFS irrespective of nodal, hormone receptor, HER2 status (although not all statistically significant) • More serious adverse events during treatment phase with TAC than FAC (36% vs 9%); more sensory neuropathy during follow-up in TAC group (4% vs 1%, p<0.0001)
Hugh, 2009[82]	BCIRG 001	See previous entry in table[80] Subtypes and response to docetaxel: 14.5% Triple negative 8.5% HER2 (HER2+, ER−, PR−) 61.1% luminal B (ER+	1350					3−y DFS (p values compared with luminal B) were 67% TN (p<0.001, HR=2.22), 68% HER2(p=0.0008, HR=2.12), 82% (referent luminal B), 91% luminal A (p=0.0027, HR=0.46) Improved 3−y DFS with TAC was found in the luminal B group (p=0.025) and a

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		and/or PR+ and either HER2+ and/or Ki-67^{high}) 15.9% luminal A (ER+ and/or PR+ and not HER2+ or Ki-67 ^{high})						combined ER+/HER− group treated with tamoxifen (p=0.041), with a marginal trend in the triple negatives (p=0.051) and HER2 (p=0.068) subtypes. No DFS advantage was found in the luminal A population.
Dumontet, 2010[83]	BCIRG 001	See previous entry in table[80] IHC assessment of biological markers	1350					No interaction with Ki-67 and treatment allocation Ki-67 and p53 protein, as well as microtubule-related parameters tau protein and tubulin III are independent prognostic factors but not predictive of docetaxel benefit
Francis, 2008[54]	BIG 02−98 1998−2001	See previously in this table (Taxane + anthracycline [sequential] vs more non-taxane [anthracycline] regimen)						
Martín, 2010[84]	GEICAM 9805 1999−2003	TAC vs FAC TAC: T (75 mg/m^2) + A (50 mg/m^2) +C (500 mg/m^2) q3w×6 FAC: F (500 mg/m^2) + A (50 mg/m^2) +C (500 mg/m^2) q3w×6 Primary prophylaxis with GCSF not permitted in original protocol, amended after 230 pts due to incidence of neutropenic fever in >25% of TAC group; all TAC pts then received GCSF; in FAC group received prophylactic antibiotics and GCSF in all remaining cycles if	1060	N0 (≥10 nodes examined), T1−3, and at least one St Gallen risk factor (T2+, ER− and PR−, histological grade 2 or 3, age <35 y)	51% T1 47% T2 2% T3	53% premenopausal 65% HR+, 35% HR−	Tamoxifen for 5 y if HR+; RT if BCS, PMRT if >5cm depending on institution guidelines	Median follow-up 77 mo DFS: 87.8% TAC vs 81.8% FAC (32% reduction), HR=0.68 (95% CI 0.49−0.93), p=0.01 Benefit in subgroups (HR status, menopausal status, age, tumour size, grade) suggested benefit of TAC vs FAC is consistent with benefit in overall population OS: 92.5% TAC vs 93.5% FAC, HR=0.76 (95% CI 0.45−1.26), not significant, but small number of events (need longer follow-up) Grade 3 and 4 adverse events 28.2% for TAC and 17% for FAC (p<0.001); most TAC-induced adverse effects ameliorated with GCSF administered as primary prophylaxis

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		episode of febrile neutropenia or infection						
Goldstein, 2008[85]	E2197 NCT00003519	AT vs AC AT: A (60 mg/m^2) + T (60 mg/m^2) q3w×4 AC: A (60 mg/m^2) + C (600 mg/m^2) q3w×4 Primary GCSF not used, received in pts with febrile neutropenia according to ASCO guidelines	2882	N1 or N0 with tumour >1 cm (at least 6 nodes removed)	66% N0 34% N1 43% T1 57% T2+ (75% ≤2.8 cm)	48% premenopausal or peri-menopausal 32% ER−PR− 3%ER−PR+ 11% ER+PR− 54% ER+PR+	Tamoxifen for 5 y if HR+; after June 2005 could switch to AI if post-menopausal; RT after BCS, PMRT at physician discretion	Median follow-up of 79.5 mo, 5−y survival rates reported DFS: 85% both arms, HR=1.02 (95% CI 0.86−1.22), p=0.78 for AC vs AT OS: 91% vs 92% AT did not improve survival rate and was associated with more adverse effects
Sparano, 2012[86] [abstract]	E2197 1998−2000	See previous entry in table	2883		Median T size 2.0 cm			Median follow-up 11.5 y, 10−y DFS, AC vs AT (HR >1 favours AT) Overall: HR=1.02 (95% CI 0.88−1.18), p=0.83 ER+: HR=0.91 (95% CI 0.76−1.10), p=0.34 ER−: HR=1.22 (95% CI 0.96−1.56), p=0.11 OS: HR=1.03 (95% CI 0.86−1.23), p=0.73 Still no significant difference in DFS or OS
Brain, 2009[87] [abstract]	RAPP-01 1999−2003	AT vs AC AT: A (50 mg/m^2) + T (75 mg/m^2) q3w×4 AC: A (60 mg/m^2) + C (600 mg/m^2) q3w×4 No prophylactic GCSF	627	Early, high-risk pN0 or limited pN+ (N1)	43% pN0	44% Ki-67 ≥25%	RT according to standard guidelines, endocrine treatment for 5 y if HR+	Closed prematurely for adverse effects in 2003 Median follow-up 64 mo 5−y TTR 91% AT vs 90.9% AC, HR=0.91 (95% CI 0.54−1.52), p=0.71 OS: 94.9 vs 94.3%
Del Mastro, 2008[88]	GONO-MIG-5 1996−2001	FEC_{21} vs EP FEC: F (600 mg/m^2) + E (60 mg/m^2)	1055	N+ (N1−2), operable	68% N1	22% HR− 69% HR+	Tamoxifen (20mg/d) for 5 y if HR+	FEC vs EP: more nausea/vomiting (85% vs 76%, p=0.0001), mucositis (46% vs 37%, p=0.003), leukopenia (52% vs 40%,

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
[abstract]		+ C (600 mg/m^2) q3w×6 EP: E (90 mg/m^2) + P (175 mg/m^2) q3w×4						p=0.0002); less anemia (17% vs 25%, p=0.006), fever (7% vs 15%, p=0.0001), myalgia (1% vs 19%, p=0.0001), neurotoxicity (6% vs 38%, p<0.0001), allergic reaction (1% vs 5%, p=0.03) Median follow-up 8.2 y EFS (5 y): 71% FEC vs 70% EP EFS (10 y): 46% both arms OS (5 y): 89% vs 88% OS (10 y): 72% vs 76%, p=0.8 Conclude different adverse effects profiles, no difference in survival rate
Roché, 2009[89] [abstract]	PACS04 2001−2004	FEC vs ET FEC: F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×6 ET: E (75 mg/m^2) + T (75 mg/m^2) q3w×6 GCSF mandatory for subsequent cycles after febrile neutropenia or treatment delay for neutropenia	3010	N+	67% N1 49% T2+	48% post-menopausal 62% ER+PR+ 20% ER−PR− 19% HER2+	RT after BCS; tamoxifen for 5 y if HR+, protocol amendments allowed sequential use of AIs; HER2+ secondarily randomized to 1 y trastuzumab or observation (see HER2+ table)	FEC vs ET adverse effects: febrile neutropenia 2% vs 6.4% of cycles, grade 3−4 neutropenia 34% vs 9%, leucopenia 35% vs 47%, thrombopenia 1.7% vs 0.3%, nausea/vomiting 14% vs 8% Median follow-up 59.3 mo; report 5−y survival rates DFS: 79.7% FEC vs 81.7% ET, HR=0.89 (95% CI 0.76−1.05), p=0.18 Positive interaction was found and favoured ET for the HER2+ subgroup, p=0.01 OS: 90.3% FEC vs 90.1% ET, HR=1.07 (95% CI 0.85−1.35), p=0.54
Gianni, 2009[90]; Zambetti, 2013[91]	ECTO 1996−2002	See neoadjuvant section later in this table						

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Taxane without anthracycline in one allocation								
Jones, 2009[92]	US Oncology Research Trial 9735 1997−2000	AC vs TC AC: A (60 mg/m^2) + C (600 mg/m^2) q3w×4 TC: T (75 mg/m^2) + C (600 mg/m^2) q3w×4 Did not use prophylactic GCSF	1016	Stage I-III, 1−7 cm,	48% NO 42% N1 10% N2+	69% HR+ 31% HR−	Tamoxifen for 5 y if HR+; RT after BCS, PMRT if N2+; HER2 status determined in 170 pts (emphasis on those who relapsed)	Median follow-up 7 y, 7−y survival rate results DFS: 81% TC vs 75% AC, HR=0.74 (95% CI 0.56−0.98), p=0.033 OS: 87% TC vs 82% AC, HR=0.69 (95% CI 0.50−0.97), p=0.032 TC was favoured in all subgroups: age, HER2 status, ER Grade 3 and 4 adverse events: more anemia and febrile neutropenia in older pts and more febrile neutropenia with TC than AC; 3 late deaths in AC group probably related to treatment
Shulman 2014, 2012[93,94]	CALGB 40101 2002−2010	P vs AC P: 80 mg/m^2 q1w×12 or 18 (N=287) or 175 mg/m^2 q2w×4 or 6(N=1653); AC; 60/600 mg/m^2 Randomized to 4 or 6 cycles (N=284 q3w, N=1647 q2w) Test of non-inferiority of T to AC (one-sided 95% CI of HR <1.30 for RFS)	3871 (4646 planned)	0−3 positive axillary nodes; operable	90% N0 65% T1 35% T2+	40% premenopausal, 68% HR+84% HER2−		Median follow-up 6.1 y RFS: HR=1.26 (1−05−1.53) favouring AC OS: HR=1.27 (1.00−1.62) favouring AC 5−y RFS 88% P vs 91% AC 5−y OS 94% P vs 95% AC OS, in table: 92% vs 94% The trial did not show non-inferiority of single agent P compared with AC Grade 3+ adverse effects (hemoglobin, neutropenia, vomiting, fatigue) higher with AC; neuropathy higher in P arm At median 5.3 y, 4−y RFS 90.9% vs 91.8% for 6 and 4 cycles, HR=1.03 (95% CI 0.84−1.28, p=0.77); OS 95.3% vs 96.3%, HR=1.12 (95% CI 0.84−1.49), p=0.44 Concluded 6 cycles not better than 4 cycles

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Nitz, 2011[95]	WSG Plan B 2009−2011 +	TC×6 vs 4EC×4 -TC×4 Pts with HR+ N0−3 and RS11 receive endocrine therapy only (not included in randomization)	2296, ongoing	HER2−; N+ or high-risk N0 (pT2, HR−, G2−3, age 35 y, or high uPa/PAI-1)				Ongoing
Ortmann, 2011[96]	SUCCESS-C	FEC×3→ T×3 vs TC×6	1452, Target 3547	HER2−				Ongoing
Nitz, 2009[66] [abstract]	WSG/AGO AM02	See previously in this table[66-69]						
Mansi, 2010[97]	Anglo-Celtic (ACCOG) 1999−2002	See neoadjuvant section later in this table						
Second-generation studies, taxane vs taxane (different dose or docetaxel vs paclitaxel)								
Citron, 2003[63]	CALGB 9741 1997−1999	I. A→ P→ C vs II. dd A→ P→ C vs III. AC→ P vs IV. dd AC→ P I. A→ P→ C: A (60 mg/m^2) q3w×4→ P (175 mg/m^2 IV over 3 hrs) q3w×4→ C (600 mg/m^2 IV) q3w×4 (33 w total) II. As I but each cycle q2w (22 w total) III. As I but C administered concurrently with A (total 21 w) IV. As II but C administered concurrently with A (total 14 w)	1973	T0−3, N1−2, M0	59% N1, 29% N2, 12% N3 (median 3 positive nodes) 40% T1, 58% T2+ 2% unknown	49% premenopausal 65% ER+	70% of female pts received tamoxifen; recommended that tamoxifen 20 mg/d be administered for 5 y to all HR+; pre-menopausal and to all post-menopausal	Median follow-up 36 mo DFS: dd (q2w) vs q3w at 3 y: 85% vs 81% RR=0.74, p=0.010 DFS, q2w vs q3 w at 4 y: 82% vs 75%, p=0.0072 OS at 3 y, q2w vs q3w: 92% vs 90%, RR=0.69, p=0.013 Treatment sequence (sequential A→ P→ C or concurrent AC→ P) was not significantly correlated with DFS (p=0.58) nor OS (p=0.48) dd + filgrastim caused less grade 4 granulocytopenia, 3% and 9% for arms II and IV (q2w) vs 24% and 43% for arms 1 and 3 (q3 w) Arm IV (AC→ T q2w) had higher rate of transfusions (13%) vs 0%, 3%, 4% on arms I,

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		Dose-dense (II and IV) received filgrastim days 3−10 of each cycle						II, III Concurrent regimens had higher Grade 3+ emesis (7% vs 3%, p=0.0002), later cardiotoxicity (2% vs 1%, p=0.11), severe neurotoxicity (4% vs 2%, p=0.005)
Budd, 2013, 2011[37,38] [abstract]	SWOG S0221 2003−2012	dd AC→ P (80 mg/m^2)q1w×12 vs dd AC→ P (175mg/m^2)q2w×6 dd AC=AC (60/600 mg/m^2) q2w×6 + pegfilgrastim Initially was initial AC vs ddAC randomization then P randomization but AC→P arms were discontinued for futility after 2716 pts and remaining pts received ddAC AC=A(24 mg/m^2)q1w×15 + C(60mg/m^2)daily + filgrastim	3294	N+ or high risk N0; operable				Powered to find DFS HR≤0.82 for weekly vs q2 weekly for each factor HR=1.08 (95% CI 0.90−1.28), p=0.42 and therefore excluding the hypothesis that HR=0.82 Estimated 5−y PFS 82% vs 81% for weekly P and ddP respectively
Loesch, 2010[98]	2000−2002	AC→ P vs AP→ P AC (60/600 mg/m^2)q3w×4→ P (175 mg/m^2) q3w×4 AP (50/200 mg/m^2)q3w×4→ P (80mg/m^2)q1w×12 No prophylactic hematopoietic growth factors permitted in cycle 1; use in subsequent cycles at physician's discretion	1830	High risk: N1−2 and T1−3, or N0 >2 cm or N0 >1cm and HR−	Stage I-III 6% Stage I 46% Stage IIA 35% Stage IIB 13% Stage IIIA 27% N0 46% N1 20% N2 8% N3	33% premenopausal 7% peri-menopausal 57% post-menopausal 52% ER+PR+ 10% ER+PR− 2% ER−PR+ 35% ER−PR− (HR−) 33% HER2+	Premenopaus-al HR+ received 2−3 y tamoxifen (later increased to 5 y), Post-menopausal pts received 2−3 y tamoxifen which could be followed by	Median follow-up 64 mo, report 6−y survival rates (median survival not yet reached), no significant difference DFS: 79% vs 80%, OS: 82% vs 87%, p=0.08 Unplanned subgroup analysis for OS: HR− and TN groups favoured arm 2 (p=0.06 and p=0.07) Both regimens equally effective and tolerable Dose-dense P (arm 2) is as effective, but increased peripheral neuropathy

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
						62% HER2− 21% TN	AI at physicians discretion; RT after BCS, PMRT if N2+	
Swain, 2010a[99]	NSABP B30 NCT00003782 1999−2004	AC→ T vs AT vs ACT AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 AT: A (60 mg/m^2) + T (60 mg/m^2) q3w×4 ACT: A (60 mg/m^2) + C (600 mg/m^2) + T (60 mg/m^2) q3w×4 Doses modified in Sept 2000 after 5 deaths were reported with ACT. ACT: A 50 mg/m^2, C 500 mg/m^2, T 75 mg/m^2 AT: A 50 mg/m^2, T 75 mg/m^2; added primary prophylaxis with GCSF in these two treatment groups	5264	pN+, cN0−1, early, T1−3	65% N1 25% N2 8% N3 3% unknown 42% ≤2cm(T1) 40% 2−4 cm 15% >4 cm	45% pre- or peri-menopausal; 75% ER+	HR+ received tamoxifen for 5 y, starting October 2002 anastrozole was allowed in post-menopausal pts Pre-menopausal for menstrual history substudy	Median follow-up 73 mo, calculated 8−y survival rates DFS: AC→ T 74% vs AT 69%, HR=0.80, p=0.001 DFS: AC→ T 74% vs ACT 69%, HR=0.83, p=0.01 OS: AC→ T 83% vs AT 79%, HR=0.83, p=0.03 OS: AC→ T 83% vs ACT 79%, HR=0.86, p=0.09 AT non-inferior to ACT for OS, HR=0.96 (95% CI 0.82−1.14) No interaction between treatment effect and factors tested (age, hormone receptor status, nodes, tumour size, hormone therapy, menopausal status) Increased incidence of grade 3 or 4 adverse events with AC→ T (65%) compared with AT (45%) or ACT (48%), including stomatitis, febrile neutropenia, infection, arthralgia, fatigue, and vomiting Concluded AC→ T reduced mortality rates, and hypothesized that longer course and/or higher dose of T are important for maximum effect Menstrual history substudy (N=2343): survival rate higher in pts with amenorrhea for

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								≥6 mo in the 24 mo after randomization: DFS RR=0.70, p<0.001, OS HR=0.76, p=0.04 No interaction for treatment, age, ER status
Swain, 2010b[100]	NSABP B30 NCT00003782	See previous entry in table[99] Reanalysis of menstrual history (MH) substudy to report 12−m landmark analysis	1885					12−m landmark analysis among female pts with amenorrhea compared with rest Significant improvement in DFS (HR=0.65, p<0.001) and OS (HR=0.72, p=0.04) ER+ subgroup: DFS HR=0.51, p<0.001; OS HR=0.52, p=0.002 ER− subgroup: DFS HR=0.96, p=0.85; OS HR=1.08, p=0.76
Ganz, 2011[101]	NSABP B30 NCT00003782 QoL 1999−2001	See previous entry in table[99] N=2145 in menstrual history (MH) substudy N=2111 in QoL substudy; calculated a trial outcome index (TOI) that summarizes physical and functional well-being scales and disease-specific items, 5− point difference is clinically meaningful, with a high score being better	5351 (2145, 2111)	MH substudy: pre-menopausal			MH substudy: 77% received tamoxifen QoL substudy: 79% received tamoxifen	Rate of prolonged amenorrhea at 12 mo differs significantly by treatment group: 70% AC→ T, 38% AT, 58% TAC (p<0.001) If exclude female pts with unknown status at 12 mo, 83% AC→ T, 47% AT, 67% TAC (p<0.001) AC→ T had higher rate of prolonged amenorrhea to 12, 18, and 24 mo compared with AT; rates higher with tamoxifen AT without tamoxifen had lowest rate of amenorrhea (20%-25% over the 24 mo of observation) Information may be useful in younger female pts interested in preserving fertility, because AT may offer better chance of return of menses QoL Outcomes: Over 24 mo, AC→ T had TOI 2.4 points lower than TAC; AT had TOI 1.0 points

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								lower than TAC; differences are statistically significant but not clinically meaningful At 6 mo, AC→ T had TOI ≈ 10 points lower than TAC or AT TAC and AT pts TOI and symptoms severity score returned to baseline at 6 mo, whereas AC→ T returned to baseline at 12 mo (p<0.001)
Eiermann, 2011[102]	BCIRG 005 2000−2003	TAC×6 vs AC×4→ T×4 TAC: T (75 mg/m^2) + A (50 mg/m^2) + C (500 mg/m^2) q3w×6 AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 Primary prophylaxis with GCSF allowed; recommend for secondary prophylaxis after an episode of febrile neutropenia or infection	3298	N+ (cN0−1 but pN+, ALND of at least 6 nodes), HER2−, T1−3	41% pT1 51% pT2 8% pT3 61% N1 28% N2, 11% N3	48% premenopausal 82% HR+	96% received adjuvant tamoxifen and/or AIs; 66% received RT	TAC associated with more febrile neutropenia and thrombocytopenia, AC→ T associate with more sensory neuropathy, nail changes and myalgia; neutropenic infection similar in both groups At median follow-up 65 mo, estimated 5−y DFS & OS DFS 79% in both groups: HR=1.0 (95% CI 0.86−1.16), p=0.98 OS 88 and 89%: HR=0.91 (95% CI 0.75−1.11), p=0.37 Conclude equally effective but different adverse effects profile
Poole, 2008[103] [abstract] Wardley, 2008[23]	tAnGo 2001−2004 safety substudy	EC→ PG vs EC→ P EC→ PG : E (90 mg/m^2 IV) + C (600 mg/m2) q3w×4→ P (175 mg/m2) + G (1250 mg/m^2 days 1 & 8) q3w×4 EC→ P (details not reported, assumed to be same as above without G)	3152 135 (safety sub-study)	Higher risk early	77% N+ 61% T2+	41% ER−, 37% PR−, 26% HER2+ (of 909 assayed)		Median follow-up 35 mo DFS: HR=1.0 (95% CI 0.8−1.2), p=0.96 OS: HR=1.1 (95% CI 0.9−1.4), p=0.35 No subset where EC→ PG more effective, including by ER/PR status Both regimens reported temporary reductions in pulmonary functions and transient transaminitis levels (not clinically significant); these were greater with EC→ PG but both well

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								tolerated
Joensuu, 2012[9]	FinXX NCT 0114816	TX→ CEX vs T→ CEF TX→ CEX: T (60 mg/m^2) + X (900 mg/m^2; days 1−15) q3w×3→ C (600 mg/m^2) + E (75 mg/m^2) + X (900 mg/m^2; days 1−15) q3w×3 T→ CEF: T (80 mg/m^2) q3w×3→ C (600 mg/m^2) + E (75 mg/m^2) + F (600 mg/m^2) q3w×3 Prophylactic GCSF not scheduled	1500	N+ or high risk N0 (T2+ and PR−)	11% N0 61% N1 28% N2+ 44% pT1 50% pT2 6% pT3−4	44% pre-menopausal 56% post-menopausal 77% ER+, 62% PR+, 19% HER2+	HR+ received adjuvant endocrine therapy for 5 y, premenopausal received tamoxifen and post-menopausal anastrozole; RT according to institutions practice; protocol amended May 2005 to allow trastuzumab for HER2+	Median follow-up 59 mo, calculated survival rates at 5 y, TX→CEX vs T→CEF DFS: 86.6% vs 84.1%, HR=0.78 (95% CI 0.59−1.03), p=0.08 OS: 92.5% vs 89.9%, HR=0.73 (95% CI 0.52−1.04), p=0.080 TX→CEX arm had significantly fewer local relapses (8 vs 20, HR=0.39, p=0.024), deaths from breast cancer (42 vs 64, HR=0.64, p=0.027), and better breast-cancer specific survival, HR=0.64, (95% CI 0.44−0.95) p=0.027) Exploratory subgroup analysis, TX→CEX vs T→CEF: RFS in N2 pts with N2 cancer (HR=0.64, 95% CI 0.43−0.96) RFS in pts with TN cancer (HR=0.48, 95% CI 0.26−0.88, p=0.018) TX/CEX was associated with more capecitabine-related adverse effects including stomatitis, hand-foot syndrome, nail changes, and diarrhea, whereas T/CEF was associated with more frequent neutropenia, febrile neutropenia, infection with neutropenia, myalgia, and amenorrhea, probably as a result of the higher docetaxel dose.
Sparano, 2008[104]	E1199, ECO 1199 NCT00004125	AC→ P (q1w×12) vs AC→ P (q3w×4) vs AC→ T (q1w×12) vs AC→ T (q3w×4) AC→ P: A (60 mg/m^2) + C (600	4950	N+ (N1−2), T1−3; or N0 and high risk T2−3	12% N0 56% N1 32% N2−3	70% HR+, 26% HR−, 4% unknown; 19% HER2+, 68% HER2−,	Tamoxifen for 5 y if HR+, modified June 2005 to allow switch to AI	No significant difference in DFS between combined groups with P vs those with T (HR=1.03, p=0.61) or between weekly vs every 3 w (HR=1.06, p=0.33) 5−y survival rates: compared with

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
	1999−2002	mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4 AC→ P: AC as above→ P (80 mg/m^2) q1w×12 AC→ T: AC as above→ T (100 mg/m^2) q3w×4 AC→ T: AC as above→ T (35 mg/m^2) q1w×12 P q3 w is considered standard therapy Colony-stimulating factors administered at physician discretion according to ASCO guidelines for pts who had an episode of febrile neutropenia or persistent neutropenia that prevented treatment on schedule				13% unknown	during or after the 5−y course; RT after BCS, PMRT at discretion of treating physician	standard therapy (P every 3 w, OS 77%), HR >1 favours experimental therapy: P (weekly) DFS: HR=1.27 (1.03−1.57), p=0.006 OS: HR=1.32 (1.02−1.72), p=0.01 Grade 2−4 neuropathies more frequent with weekly P (27% vs 20%) T (every 3 w) DFS: HR=1.23 (1.00−1.52), p=0.02 OS: HR=1.13 (95% CI 0.88−1.46), p=0.25 T (weekly) DFS: HR=1.09 (95% CI 0.89−1.34), p=0.29 OS: HR=1.02 (95% CI 0.80−1.32), p=0.80 Interaction of T and weekly schedule (q1w or q3w) was significant In exploratory analysis, both HER2+ and HER2− subgroups did better on experimental treatment, but only significant for HER2− on weekly P (DFS, HR=1.33, p=0.009; OS, HR=1.34, p=0.03; not affected by hormone receptor status) Overall, weekly P after AC improved DFS and OS
Schneider, 2012[105]	E1199	See previous entry in table	4554					Median time to neuropathy after first dose of taxane was 3.0 mo (range 0−57 mo) Grade 2−4 neuropathy developed in 18%, 22%, 15%, 13% of pts in group P3 (P q3w), P1 (P q1w), D3 (T q3w), D1 (T q1w), respectively P1 vs P3, OR=1.34 (1.09−1.64), p=0.006

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								D1 vs P3 OR=0.73 (95% CI 0.58−0.92), p=0.008 D3 vs P3 OR=0.81 (95% CI 0.65−1.02), p=0.070
Watanabe, 2009[106] [abstract, poster]	N-SAS-BC02 2000−2006	a) (AC or EC)→ P vs b) (AC or EC)→ T vs c) P vs d) T (AC or EC)→ P: A (60 mg/m^2) or E (75 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4 (AC or EC)→ T: (AC or EC) as above→ T (75 mg/m^2) q3w×4 P: P (175 mg/m^2) q3w×8 T: T (75 mg/m^2) q3w×8	1060	N+ (SLNB or ALND); excluded ER+PR+ until June 2003	12% I 40% IIA 38% IIB 10% IIIA 64% <3 cm 36% ≥3 cm 58% N1 26% N2 16% N3	56% ER+ 44% ER− 44% PR+ 56% PR−	RT after BCS HR+ : 20mg TAM or an AI for 5 y	Trial to test non-inferiority for DFS, median follow-up 46.5 mo DFS: HR=0.81(95% CI 0.64−1.03), p=0.08 for T vs P (b or d) vs (a or c) DFS: HR=1.26 (95% CI 0.99−1.60), p=0.67 for (taxane, c or d) vs (AC-taxane, a or b) HER2+: DFS HR1.85 (1.11−3.07), p=0.017 HER2−: 1.11 (95% CI 0.85−1.46), p=0.44 Grade 3−4 adverse effects lowest in P arm Neutropenic fever more frequent with T than P Conclude DFS better with T than P AC improves DFS in subset with HER2+ but not HER2− Severe adverse effects greater with T than P
Shiroiwa, 2011[107]	N-SAS BC 02 2001−2003	See previous entry in table	299 QoL sub-study	N+, Stage I-IIIA, excluded ER+PR+	55% N1 27% N2 18% N3 56% <3 cm 44% ≥3 cm	25% HER2+ 44% HER2− 34% unknown 39% HR+ 61% HR−	Utility scores for health-related QoL, range 0−1 (1 is perfect health)	• Utility scores significantly lower with T alone (group d) than AC (groups a and b) • AC-taxane had significantly higher utility score than taxane alone • No difference between T (b or d) vs P (a or c)
Shimozuma 2012[108]	N-SAS BC02	See previous entry in table Study of chemotherapy-induced peripheral neuropathy (CIPN) and health-related QoL (HRQoL) assessment in first 300 pts						Author conclusions inconsistent with data, wide variation at baseline and inconsistency between groups, measured at end of cycle 6 but not cycle 8 (last cycle) so cumulative effect unknown; tests appear not sensitive enough to distinguish group

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
								differences
Swain, 2012, 2013 109,110	NSABP B-38 2004−2007	dd AC→ PG vs dd AC→ P vs TAC AC→ PG: A (60 mg/m^2) + C (600 mg/m^2) q2w×4→ P (175 mg/m^2) + G (2000 mg/m^2) q2w×4 AC→ P: AC as above→ P (175 mg/m^2) q2w×4 TAC: T (75 mg/m^2) + A (50 mg/m^2) + C (500 mg/m^2) q3w×6 Primary GCSF required; erythopoiesis-stimulating agents (ESA) used at investigator discretion	4894	Operable, N+	65% N1	52% post-menopausal 80% HR+		Median follow-up 64 mo, reported 5−y survival rates DFS: 80.6% AC→ PG vs 82.2% AC→ P (HR=1.1, p=0.27) and 80.1% TAC (HR=0.97, p=0.71) DFS: AC→ P vs TAC, HR=0.89, p=0.14 OS: 90.8% AC→ PG vs 89.1% AC→ P (HR=0.89, p=0.25) and 89.6% TAC (HR=0.90, p=0.32) OS: AC→ P vs TAC, HR=1.01, p=0.92 Adverse effects for TAC, AC→ P, AC→ PG respectively: febrile neutropenia (grade 3−4, 8%, 2%, 2%, p<0.001); sensory neuropathy (grades 3−4, <1%, 7%, 6%, p<0.001), diarrhea (grade 3−4, Hgb <10 in 12%, 26%, 33% with ESA use in 35.2%, 46%, 51.6% and transfusions in 3.7%, 6.3%, 9.4%; death on treatment (N=13, 5, 7, p=0.2) Conclude no significant differences in efficacy although adverse effects profiles differed
Pippen, 2011[15] O'Shaughnessy, 2010[16]	US Oncology 1062 USON 01062	AC→ T vs AC→ TX AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4	2611	Resectable, early, high risk (N+, T1−3; or N0, T2+; or N0, >1 cm, HR−)			Tamoxifen or AI for 5 y if HR+; After 2005, HER2+ offered 1 y	Median follow-up of 5 y, 304 events DFS: HR=0.84 (95% CI 0.67−1.05), p=0.125 [endpoint not met] Distant DFS favoured TX group: HR=0.80 (95% CI 0.63−1.02), p=0.067 OS: improvement with TX vs T:

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
[abstracts]	2002−2006	AC→ TX: AC as above→ TX (T: 75 mg/m^2 day 1, X: 825 mg/m^2 bid, days 1−14) [number of cycles not reported]					trastuzumab	HR=0.68 (95% CI 0.51−0.92), p=0.011 Subgroup analysis appeared to favour TX over T Unplanned subset analysis of Ki-67 expression and DFS suggests benefit of X in more highly proliferative tumours (for Ki-67 >10%, hazard ratio for TX vs T is HR=0.70 (95% CI 0.50−0.98) for DFS and HR=0.52 (95% CI 0.33−0.82) for OS Adverse events similar in both arms, except grade 3 hand-foot syndrome (3.8% T vs 18.1% TX), grade 3/4 stomatitis (4.5% vs 9.1%), diarrhea (2.9% vs 5.1%) and febrile neutropenia (13.1% vs 9.4%)

O'Shaughnessy, 2012[17] [abstract]	USON 01062	See previous entry in table				2195 ductal
						355 lobular or mixed
								Exploratory analysis by histology:
								• Ductal pts AC→ T vs AC→ XT:
								  • No difference in DFS (HR=0.92, p=0.48) or OS (HR=0.75, p=0.07)
								• Lobular/mixed AC→ XT vs AC→ T
								  • DFS, HR=0.55, p=0.055
								  • OS, HR=0.38, p=0.04

Moebus, 2010[111] Moebus, 2011[112] [abstract]		Intense dose-dense ECP vs conventional EC→ P IDD: E→ P→ C: E (150 mg/m^2) q2w×3→ P (225 mg/m^2) q2w×3→ C (2500 mg/m^2) q2w×3 EC→ P: E (90 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4	1284	High risk, N2+ (minimum 10 nodes removed), Stage II-IIIA	58% N2 42% N3 30% pT1 55% pT2 14% pT3	48% premenopausal 72% ER+ 69% PR+ 25% HER2+, 58% HER2−, 18% unknown	Radiation of the supra-clavicular, infraclavicular and parasternal lymph nodes, as well as radiation of the breast for BCS or chest	Median follow-up 62 mo: 5−y survival rate results, dose-dense vs conventional DFS: 70% dose-dense vs 62% conventional, HR=0.72 (95% CI 0.59−0.87), p<0.001 OS: 82% vs 77%, HR=0.76 (95% CI 0.59−0.97), p=0.029 Dose-dense therapy associated with significantly more non-hematological and hematological adverse effects Conclude dose-dense ECP less well

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		Filgrastim received every dose-dense cycle but not conventional; dose-dense pts also randomized to receive epoetin alfa					wall for mastectomy recommended in all pts. HR+: 5 y tamoxifen; then 5 y letrozole if post-menopausal	tolerated but significantly improved survival Median follow-up 8 y, dose-dense vs conventional: 8 pts vs 0 developed acute myeloid leukemia or myelodysplastic syndrome Relapse : 231 pts vs 285 pts, HR=0.71 (95% CI 0.59−0.84), p<0.0001 RFS: 62% vs 51% OS: 71% vs 65%, HR=0.76 (95% CI 0.62−0.93), p=0.0086 Results independent of hormone receptor, menopausal, HER2 expression status, and number of positive nodes
Bermejo, 2013[18]	GEICAM 2003−10 2004−2007	ET→ X vs EC→ T ET (90/75 mg/m^2)q3w×4→ X (1250 mg/m^2 bid d1−14) q3w×4 EC (90/600 mg/m^2)q3w×4→ T (100 mg/m^2)q3w×4	1384	T1−3/N1−3 operable	66% N1, 25% N2, 9% N3	Stratified by site, menopausal status, number of nodes (1−3, 4−9, 9+), hormone receptor status	HER2+ pts excluded after first 803 pts recruited; 84% HR+, 11% HER2+	After median follow-up 6.6 y, survival rates at 5 y: • DFS: 82% EC→ X vs 86% EC→ T, HR=1.314 (1.042−1.657), p=0.0208 • OS not different: HR=1.113 (95% CI 0.809−1.531), p=0.511 EC→ X vs EC→ T : Neutropenia 10% vs 19%, hand-foot syndrome 20% vs 2%, diarrhea 11% vs 3%
Kelly, 2012[113]	NCT00050167 2002−2008	P→ FEC vs TX→ FEC P→ FEC: P (80 mg/m^2) q1w×12→ F (500 mg/m^2) + E (100 mg/m^2) + C (500 mg/m^2) q3w×4 TX→ FEC: X (1500 mg/m^2; days 1−14) + T (75 mg/m^2) q3w×4→ FEC as above	601	Operable. High risk eligible for adjuvant therapy; include pN2a and pN3a, exclude pN2b, cN2, cN3, T4	12% Stage 1 47% Stage IIA 26% Stage IIB 10% Stage IIIA 4% Stage IIIB-C	45% premenopausal 71% ER+ 54% PR+ 6% HER2+ 25% TN excluded HER2+ after 2005	71% received adjuvant endocrine therapy, 72% received adjuvant RT	pCR: 19.8% TX vs 16.4% P, p=0.48 Median follow-up 50 mo, was 64 RFS events RFS: 87.5% TX vs 90.7% P, p=0.51 RFS, preoperative chemotherapy: 81.5% TX vs 85.5% P, p=0.65 RFS, adjuvant chemotherapy: 90.9% TX vs 93.5% P, p=0.66 OS: 92.2% XT vs 95% P, p=0.39 Hematological and non-hematological adverse

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		Further stratified by timing of chemotherapy (preoperative, N=110 per group vs adjuvant, N=190 per group) Stopped accrual at annual safety/efficacy review when 35 RFS observed (median follow-up 40 mo) and it was highly unlikely to find a difference among treatments		(except limited T4 lesions, e.g., focal extension with negative margins). For preoperative portion must have clinically palpable disease in breast or axilla, exclude Stage I (T1N0).				effects were significantly higher in the XT arm Conclude no difference in efficacy; XT associated with higher GI, skin, neutropenic-related adverse effects
Hofmann, 2013[114]	ADAPT HR+/HER2− Started 2012−	Neoadjuvant endocrine therapy (3 w; optional if N2/3 or RS ≥26) then randomize high-risk groups to Arm A or B chemotherapy (adjuvant or neoadjuvant), both with endocrine therapy as before $Paclitaxel_{175}$ q2w×4→ EC q2w×4 vs $nab\text{-}paclitaxel_{125}$ q1w×8→ EC q2w×4	4000 planned	HR+ HER2−		High risk=N2/3; or N0/1 with RS ≥26; or N0/1 with RS 12−25 and Ki-67 ≥10% post neoadjuvant endocrine therapy		Ongoing, started 2012
Hofmann, 2013[114]	ADAPT Triple negative 2012 -	Neoadjuvant therapy (12 w): nab-paclitaxel + gemcitabine vs nab-paclitaxel + carboplatin	336 planned	Triple negative (HR− HER2−)				Ongoing, started 2012
Neoadjuvant								
Untch, 2011a[115]	PREPARE (prognosis)	**Neoadjuvant** EC→ P→ surgery (control) vs dd E→	714	T2+, included inflammatory	57% ypN0 43% ypN+	68% HR+ 32% HR−		Estimated at 3−y EC→ P compared with dd E→ dd P→ CMF

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
	2002−2005	dd P→ CMF→ surgery EC→ P→ surgery: E (90 mg/m^2) + C (600 mg/m^2) q3w×4→ P (175 mg/m^2) q3w×4→ surgery E→ P→ CMF→ surgery: E (150 mg/m^2) q2w×3→ P (225 mg/m^2) q2w×3→ C (500 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×3→ surgery Pts in both groups randomized to receive darbepoetin (DA) or none DA: 4.5 µg/kg body weight q2w starting with first dose E until 14 d after last dose of P, + 200mg oral iron (Fe^{2+}) daily dd pts received pegfilgrastim (6 mg SC on day 2 of cycles 1−6 (E_{dd}→ P_{dd}); primary prophylactic use of pegfilgrastim during CMF or in the EC→ T arm was not mandatory; filgrastim (5 µg/kg body weight daily) administered in cases of leucopenia for ≥3d, fever>38.5 C or infection and then pegfilgrastim administered prophylactically in remaining cycles			68% <4 cm 32% ≥4 cm 8% T4 (including inflammatory)			DFS 76% vs 79%, HR=1.14, p=0.37 OS 88% vs 92%, HR=1.26, p=0.237 Estimated at 3 y, with vs without darbepoetin DFS 74% vs 80%, HR=1.31, p=0.061 OS 88% vs 92%, HR=1.33, p=0.139 Pts with pCR vs without pCR DFS: 89% vs 75%, HR=2.27, p=0.001 Concluded neoadjuvant dose-intensified chemotherapy did not improve DFS, darbepoetin might have detrimental effect
Untch, 2011b[116]	PREPARE (pCR)	See previous entry in table[115]	733	T2+, included inflammatory	50% cN0 38% cN+	42% HR+ 20% HR−	91% of pts had surgery	13.2% of control and 18.7% of dose-dense group had pCR (p=0.043)

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
			714 treated		12% unknown 88% cT1−3 8% cT4 65% T <4 cm 30% T ≥4 cm	38% missing 42% HER2, 0−1+ 39% HER2, 2+ 8% HER2, 3+ 10% missing	after chemotherapy	10% control,17.4% dose-dense group had cCR DA did not affect pCR, clinical response, or nodal response (p=0.972) In TN subgroup, pCR 44.6% with dose-dense vs 30.4% control (p=0.12) Both chemotherapy groups had had significant decrease in hemoglobin levels; no change in DA+ group DA+ group had more thromboembolic events (6% vs 3%, p=0.055) Hematological adverse effects generally mild, similar in all treatment groups Grade 3−4 sensory neuropathy, neurological complaints, mucositis/stomatitis/proctitis were significantly higher in dose-dense group Conclude: neoadjuvant dose-dense superior in terms of pCR, darbepoetin did not influence response
Gianni, 2009[90]	ECTO 1996−2002	Arm A: surgery→ A→ CMF vs Arm B: surgery→ AP→ CMF vs Arm C: AP→ CMF→ surgery (neoadjuvant) Arm A: A (75 mg/m^2) q3w×4→ C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days 1&8 q4w×4 Arm B & C: A (60 mg/m^2) + P (200 mg/m^2) q3w×4→ C (600 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) days	1355	T2−3, N0−1	54% N0 46% N1−2 80% ≤4 cm 20% >4 cm	68% HR+ 31% HR−	RT after BCS; tamoxifen offered to all pts at start, only HR+ pts after July 2000	After follow-up 76 mo, report 7−y survival rates: Arm B vs Arm A DFS: 76% vs 69%, HR=0.73 (95% CI 0.57−0.97), p=0.03 OS: 85% vs 82%, HR=0.80 (95% CI 0.56−1.14), p=0.21 Arm B vs Arm C DFS: 76% vs 72%, HR=1.21 (95% CI 0.92−1.60), p=0.18 OS: 85% vs 84%, HR=1.10 (95% CI 0.77−1.59), p=0.60 BCS: 63% arm C vs 34% arm A/B,

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		1&8 q4w×4						p<0.001 Study not powered for OS
Zambetti, 2013[91] [abstract]	ECTO	See previous entry in table	1335					10 y results, arm B (AP→ CMF) vs arm A • Freedom from progression (FFP): HR=0.77, p=0.045 • OS: HR=0.82, p=0.24 (no difference) Arm B vs Arm C (adjuvant vs neoadjuvant) • Freedom from progression: HR=0.79, p=0.07 Primary chemotherapy (arm C) allowed BCS in a significant percentage of pts
Kaufmann, 2010[117] [abstract/ poster] Darb-Esfahani, 2009[118]	GeparDuo NCT00793377 1999−2001	Preoperative dose-intensified AT×4 vs preoperative AC×4→ T×4 AT: T (50 mg/m^2) + A (75 mg/m^2) q2w×4 AC→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4 GCSF administered with AT	913	T2−3, N0−2, M0	0.8% T1 84% T2 15% T3 60% N0 40% N+	28% ER−PR− 72% ER+ and/or PR+	All received tamoxifen	Preoperative AC→ T is superior for pCR 14.3% vs 7%, OR=2.22 (95% CI 1.41−3.49), p<0.001 Median follow-up 64.3 mo; 5−y DFS and OS reported DFS: AC→ T 65% vs AT 69%; HR=1.11 (95% CI 0.884−1.40), p=0.36 OS: 84% in both arms
Untch, 2009[119]	AGO 1 1998−2002	Preoperative E+P vs intense dose-dense (IDD) E→ P E+P: E (90 mg/m^2) + P (175 mg/m^2) q3w×4 IDD: E→ P: E (150 mg/m^2) q2w×3→ P (250 mg/m^2) q2w×3; all received filgrastim (5µg/kg) on days 3−10 of each cycle All received 3 cycles of CMF after surgery; C (500 mg/m^2) + M (40 mg/m^2) + F (600 mg/m^2) on days 1&8	668	High risk: 85% ≥3 cm; 15% inflammatory	34% N0 54% N+ 12% unknown 53% T2 29% T3 18% T4	68% HR+ 49% <50 y old	Tamoxifen (20 mg/d for 5 y) administered if HR+; RT for all BCS, PMRT where indicated	IDD vs conventional, median follow-up 55 mo Improved pCR rate (18% vs 10%, p=0.008) DFS: HR=0.71 (95% CI 0.54−0.92), p=0.011 OS: HR=0.83 (95% CI 0.69−0.99), p=0.041 Inflammatory cancers DFS: HR=1.10, p=0.739; OS: HR=1.25, p=0.544 Non-inflammatory cancers DFS: HR=0.65 (95% CI 0.48−0.88), p=0.005

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
		q4w *after surgery*.						OS HR=0.77 (95% CI 0.63−0.95), p=0.013 IDD associated with significantly more nonhematological adverse effects, anemia, and thrombocytopenia, but similar neutropenia and infection rates
Rastogi, 2008[44]	NSABP B-27 1995−2000	Preoperative AC→ surgery vs preoperative AC→ T→ surgery vs preoperative AC→ surgery→ T AC→ surgery: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ surgery AC→ T→ surgery: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ T (100 mg/m^2) q3w×4→ surgery AC→ surgery→ T: A (60 mg/m^2) + C (600 mg/m^2) q3w×4→ surgery→ T (100 mg/m^2)×4	2344	T1c-3, N0−1; or T1−3, N1	70% N0 30% N+ 14% T1 58% T2 28% T3		RT after BCS, PMRT not allowed All groups:→ Tamoxifen (20mg/day) for 5 y initiated on first day of chemotherapy	After median follow-up 8.5 y, no statistically significant differences in DFS or OS DFS: group 2 vs 1: HR=0.92 (95% CI 0.78−1.08), p=0.29 DFS: group 3 vs 1: HR=0.92 (95% CI 0.78−1.08), p=0.29 OS: p=0.76 across all 3 arms Addition of T did not significantly impact DFS (HR=0.93, 0.92, p=0.29) or OS (HR=0.93 and 0.97, p=0.46 and 0.76) Preoperative AC→ T significantly increased clinical response (91% vs 86%, p<0.001), cCR (63% vs 40%, p<0.001), and pCR (26% vs 13%, p>0.001)compared to preoperative AC Pts with pCR had significantly superior DFS and OS (8−y follow-up) DFS: HR=0.49, p<0.001, OS: HR=0.36, p<0.001
Mansi, 2010[97] Evans, 2005[120]	Anglo-Celtic (ACCOG) 1999−2002	Neoadjuvant AC vs AT AC: A (60 mg/m^2) + C (600 mg/m^2) q3w (6 cycles maximum) AT: A (50 mg/m^2) + T (75 mg/m^2) q3w (6 cycles maximum) 6% did not receive surgery after neoadjuvant chemotherapy	363	Large tumours (≥3cm), inflammatory, or LABC considered candidates for primary	Before chemotherapy: 77% operable 15% inflammatory 8% LABC			pCR: 24% AC vs 21% A, p=0.61 cCR: 17% AC vs 20% AD, p=0.42 overall clinical response: 61% AC vs 70% AD, p=0.06 5−y survival rates DFS: 54% AC vs 59% AD, p=0.20 OS: 67% AC vs 72% AD, p=0.24

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
				chemotherapy	Median 6 cm			
Lee, 2008[39]	2002−2005	Neoadjuvant TX→ surgery→ AC vs Neoadjuvant AC→ surgery→ TX	204	N+, Stage II/III	Stage II/III 77% T1−2, 23% T3−4 69% N1, 31% N2−3	61% HR+ 34% HER2+ 47% HER2− 18% unknown	All received RT; tamoxifen or anastrozole if HR+	At median follow-up of 37 mo, no significant difference in DFS by treatment groups (p=0.932). Compared with AC, TX increased pCR in primary tumours (21% vs 10%, p=0.024) and clinical response (84% vs 65%, p=0.003). Fewer pts developed recurrence who achieved pCR in lymph node (LN); HR=0.189 (95% CI 0.044−0.815), p=0.025 in the multivariate analysis. TX was associated with less nausea and vomiting, but more stomatitis, diarrhea, myalgia, and skin/nail changes than AC
Earl, 2014[24]	Neo-tAnGo	Neoadjuvant: EC→ P vs P→ EC vs EC→ GP vs GP→ EC Effect of gemcitabine and role of sequence (EC→ P vs P→ EC) stratified by ER status, tumour size (50 mm cut-off), nodal status (N0/N+), inflammatory/locally advanced (yes/no)	831	Early invasive, >2 cm; no previous chemo, RT, endocrine therapy T4 eligible	80% T2, 20% T3 50% N+	67% ER+ 51% PR+ 25% inflammatory or LABC; 57% premenopausal , 6% peri-menopausal		Median follow-up 47 mo; first planned interim analysis found no significant difference in DFS or OS • DFS : EC→ P vs EC→ PG HR=1.13 (95% CI 0.88−1.46), p=0.34; P→ EC vs EC→ P HR=0.84 (95% CI 0.65−1.09), p=0.18 • OS: EC→ P vs EC→ PG HR=1.02 (95% CI 0.76−1.39), p=0.89; P→ EC vs EC→ P HR=0.82 (95% CI 0.60−1.11), p=0.19 • pCR greater with P→ EC than EC→ P (20% vs 15%, p=0.03); G did not increase pCR • pCR was correlated with significant improvement in DFS (p<0.001) and OS (p=0.0007)
Von Minckwitz, 2008, 2013[121-]	GeparTrio 2002−2005	TAC vs NX if poor response to TAC 2 cycles TAC then evaluated response; early responders	2012	Tumour ≥2 cm; at least one risk factor of age <36 y,	61% T2, 19% T3, 12% T4a-c, 5% T4d; median 40	LABC, inflammatory, N3 including or supraclavicular		Median follow-up 62 mo • Early responders: DFS better for TAC×8 than TAC×6 (HR=0.78, 95% CI 0.62−0.97,p=0.026) • Early non-responders: DFS better for

Author, year	Trial name, enrolment period	Intervention	# pts	Inclusion criteria	Staging	Other characteristics*	Other	Results
124		randomized to 4 (N=704) or 6 (N=686) additional cycles TAC If no sonographic response (reduction in product of 2 largest perpendicular diameters was <50%) then randomized to 4 additional cycles TAC (N=321) or vinorelbine + capecitabine (NX; N=301); excluded those with disease progression		<5 cm, ER−PR−, N+, undifferent-iated grade	mm by palpation and 29 mm by sonography; 42% N0	nodes were assigned within a separate stratum		TAC→NX than TAC×6 (HR=0.59, 95% CI 0.49−0.82, p=0.001); • DFS for non-responders administered TAC→NX similar to early responders administered TAC×8 • Response-guided therapy (TAC×8 or TAC→NX) better than TAC×6 for DFS overall (HR=0.71, p<0.003) and for subgroups HR+ (luminal A, luminal B) but not HR− or TN pCR predicted improved DFS in TN, HER2+ (nonluminal) and luminal B (Her2−) • Adverse effects: NX had more hand-foot syndrome and sensory neuropathy but less hematological adverse effects, mucositis, infections, and nail changes • Post-treatment (after 2 cycles TAC) Ki-67 levels gave prognostic information for pts with HR+ cancer with residual disease after neoadjuvant chemotherapy (high Ki-67 had higher risk for relapse or death, p<0.0001)
Hofmann, 2013[114]	ADAPT HR+/HER2 −; ADAPT Triple negative 2012 −	See previously in this table (second-generation studies)						Ongoing, started 2012

Abbreviations: A, doxorubicin (Adriamycin); AC, doxorubicin + cyclophosphamide; ALND, axillary lymph node dissection; AT, doxorubicin + docetaxel; BCS, breast-conserving surgery; BCT, breast conserving therapy (BCS +RT); cCR, clinically complete response; CEF, cyclophosphamide + epirubicin + fluorouracil; CEX, cyclophosphamide + epirubicin + capecitabine; C, cyclophosphamide; CMF, cyclophosphamide + methotrexate + fluorouracil; dd, dose-dense; DDFS, distant disease-free survival rate; DFS, disease-free survival rate; E,

epirubicin; EC, epirubicin + cyclophosphamide; EFS, event-free survival rate; EGFR, epidermal growth-factor receptor; ER, estrogen receptor; ET, epirubicin + docetaxel; F, 5−fluorouracil; FAC, fluorouracil + doxorubicin + cyclophosphamide; FEC, fluorouracil + epirubicin + cyclophosphamide; G, gemcitabine; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, Hormone receptor positive; HR−, hormone receptor negative; HRQoL, health-related quality of life; IDD, intensive dose-dense; IDFS, invasive disease-free survival rate; IHC, immunohistochemistry; LRR, locoregional recurrence; LVI, lymphovascular invasion; N0, no positive nodes; N+, positive nodes found; N1, 1−3 positive nodes; N2, 4−9 positive nodes; N3, 10+ positive nodes; nab-paclitaxel, nanoparticle albumin-bound-paclitaxel; NX, vinorelbine + capecitabine; OS, overall-survival rate; P, paclitaxel; pCR, pathologically complete response; PMRT, postmastectomy radiation therapy; PR, progesterone receptor; pts, patients; QoL, quality of life; RFS, recurrence-free survival rate; RR, relative risk; RT, radiation therapy; T, docetaxel (Taxotere); TAC, docetaxel + doxorubicin + cyclophosphamide; TN, triple negative (PR−,ER−, and HER2−); TOI, trial outcome index; TTR, time to recurrence; TX, docetaxel + capecitabine; X, capecitabine

*HER2, ER/PR, lymph node, risk, menopausal status

Intrinsic subtypes: luminal A=(ER+ and/or PR+) and not (HER2+ or Ki-67^{high}); luminal B=(ER+ and/or PR+) and either (HER2+ and/or Ki-67^{high}); HER2=HER2+ and ER−; triple negative (TN)=PR− and ER− and HER2−; basal=TN and either (EGFR+ or cytokeratins 5/6+)

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Supplementary Appendix 1: Literature Search Strategy

1. (exp Breast Neoplasms/ or exp breast tumour/ or exp breast cancer/ or breast cancer.mp. or breast neoplasm:.mp. or ((cancer: or neoplasm: or tumo?r: or carcinom:) and (breast or mammar:)).mp)

2. exp chemoradiotherapy/ or exp chemotherapy, adjuvant/ or exp neoadjuvant therapy/ or exp adjuvant therapy/ or exp cancer hormone therapy/ or exp cancer adjuvant therapy/ or exp cancer combination chemotherapy/ or exp aromatase inhibitors/ or exp antineoplastic agents/ or (adjuvant or neoadjuvant or chemotherapy or hormonotherapy).mp.

3. **(Anthracycline#** or doxorubicin or Adriamycin or epirubicin or Ellence or **Alkylating agent#** or cyclophosphamide or Cytoxan or Neosar or Fluorouracil or 5-fluorouracil or 5-FU or Adrucil or methotrexate or amethopterin or Mexate or Folex or Rheumatrex or gemcitabine or Gemzar or **Taxane#** or docetaxel or Taxotere or paclitaxel or Taxol or Abraxane or carboplatin or Paraplatin or cisplatin or Platinol or TAC, ACMF, ACT, ATC, CAF, FAC, CEF, CMF or **Anti-estrogens or Selective Estrogen Receptor Modulator: or SERM:** or **Endocrine Therapy** or tamoxifen or Nolvadex or Apo-Tamox or Tamofen or Tamone or **Aromatase Inhibitor#** or anastrozole or Arimidex or exemestane or Aromasin or letrozole or Femara or fulvestrant or Faslodex or **HER2 inhibitor:** or trastuzumab or Herceptin or lapatinib or Tykerb or **Antiangiogenesis:** or bevacizumab or Avastin or **Granulocyte colony stimulating factor** or GCSF or Pegfilgrastim or Neulasta or filgrastim or Neupogen or **Bisphosphonate:** or Pamidronate or Aredia or zoledronic acid or Zometa).mp

4. Ovariectomy/ or exp gonadotropin-releasing hormone/ or exp gonadorelin derivative/ or exp luteinizing hormone/ or (ovariectomy or (ovar: adj3 ablation) or (ovar: adj3 suppression) or (ovar: adj3 irradiation)).mp or (gnrh or gonadorelin or lhrh agonist or lhrn analog or leuprolide or buserelin or triptorelin or Lupron or goserelin or Zoladex or Trelstar).mp

5. exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp randomized controlled trials as topic/ or exp phase 2 clinical trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/ or exp clinical trials, phase II/ or exp clinical trials, phase III/ or exp clinical trials, phase IV/ or (randomized controlled trial or clinical trial, phase III or clinical trial, phase II).pt. or (random$ control$ trial? or rct or phase II or phase III or phase IV or phase 2 or phase 3 or phase 4).tw. or ((exp clinical trial/ or exp "clinical trial (topic)"/ or exp controlled study/ or clinical trial$.mp. or clinicaltrial$.mp.) and (random$.tw. or randomization/)) or (random$ adj3 trial$).mp. or randomization/ or "clinicaltrials.gov".mp

6. (meta-analysis.mp. or meta-analysis/ or meta-analysis.pt. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or (cochrane or MEDLINE or EMBASE or cancerlit).ti. or (hand search or hand-search or manual search).ti. or practice guideline$.mp. or Practice Guideline/ or practice guideline.pt. or practice parameter:.tw)

1 and (2 or 3 or 4) and (5 or 6), limit to yr="2008 -Current", and duplicates removed

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