Supplemental Materials for

Systemic targeted therapy for her2-positive early female breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline

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Supplementary Table 1. Summary of Recommendations in Other Clinical Practice Guidelines

Guideline	Search Date, other details	Recommendations

NICE. Early and locally advanced breast cancer: diagnosis and treatment[1]	June 2008	• Offer trastuzumab, administered at three-week intervals for one year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to patients with HER2-positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable.
		• Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to patients who have any of the following:
		  • a left ventricular ejection fraction (LVEF) of 55% or less
		  • a history of documented congestive heart failure
		  • high-risk uncontrolled arrhythmias
		  • angina pectoris requiring medication
		  • clinically significant valvular disease
		  • evidence of transmural infarction on electrocardiograph (ECG)
		  • poorly controlled hypertension
		• Repeat cardiac functional assessments every three months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to <50%, then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman.

PEBC #1-24: The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/ neu-overexpressing Breast Cancer[2]	May 2006, update Sept 2009; original recommendation endorsed 2010	• Trastuzumab should be offered for one year to all patients with HER2 positive node- positive or node-negative, tumour >1 cm in size, and primary breast cancer and who are receiving or have received (neo)adjuvant chemotherapy. Trastuzumab should be offered after chemotherapy.

Guideline	Search Date, other details	Recommendations
PEBC #1-17: The Role of HER2/neu in Systemic and Radiation Therapy for Women with Breast Cancer [archived][3]	Dec 2005; Guideline archived 2011	• Patients with HER2/neu-positive breast cancer should be considered for chemotherapy containing an anthracycline instead of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or melphalan and 5-fluorouracil (PF) chemotherapy. • Although the current evidence does not support a definitive recommendation regarding tamoxifen therapy and HER2/neu status, the weight of the evidence, especially the Gruppo Universitario Napoletano (GUN) trial, suggests that the efficacy of tamoxifen may be greater in patients with HER2/neu-negative cancer than with HER2/neu-positive cancer. However, the evidence does not support a recommendation against tamoxifen therapy in patients with HER2/neu-positive cancer. While it is possible that tamoxifen is more effective in patients with HER2/neu-negative cancer, there is still sufficient evidence that it is effective in patients with HER2/neu-positive cancer as well.
National Breast Cancer Centre (NBCC) (now Cancer Australia). Recommendations for use of Trastuzumab (Herceptin) for the treatment of HER2-positive breast cancer[4]	Up to ≈ 2006	• Patients should be informed of the potential side effects of trastuzumab and any uncertainties about long-term effects. Patients receiving trastuzumab should be reviewed regularly and monitored for side effects by clinicians familiar with the drug. • Adjuvant trastuzumab should be offered with chemotherapy following surgery in patients with node positive or node negative tumours larger than 1 cm. Trastuzumab concurrently with an anthracycline is not recommended due to risk of cardiotoxicity. Trastuzumab can be offered to patients who require radiotherapy, although long-term toxicity is unknown.

Supplementary Table 2. HER2+ plus Trastuzumab, Lapatinib, and/or Pertuzumab RCTs

Study	Trial arms	N	Characteristics	Outcome
Neoadjuvant trastuzumab, lapatinib, or pertuzumab				

NeoALTTO
BIG 01−06
EGF 106903
NCT00553358[5,6]
2008−2010
	Oral lapatinib vs IV trastuzumab vs lapatinib + trastuzumab
	
	Anti-HER2 for 6 w → weekly paclitaxel + anti-HER2 for 12 w→ surgery→adjuvant FEC→ same anti-HER2 as previously for 52 w
		455	HER2+, >2 cm,	• Pathologically complete response (pCR) higher in lapatinib + trastuzumab group than trastuzumab alone (51.3% vs 29.5%, p=0.0001)
				• pCR similar (p=0.34) in lapatinib and trastuzumab groups
				• No major cardiac dysfunctions, grade 3 diarrhea and liver-enzyme alterations greater in lapatinib groups
				• Conclude dual inhibition might be a valid approach
				• Lapatinib + trastuzumab, lapatinib, trastuzumab arms:
				  • Grade 3 diarrhea 21.1%, 23.4%, 2.0%
				  • Grade 3/4 hepatic effects 10.6%, 18.1%, 7.4%
				  • Grade 3/4 neutropenia 8.5%, 15.6%, 2.6%
				  • Grade 3 skin disorders 6.6%, 6.5%, 2.7%
				• Secondary endpoints of DFS and OS rates not reported yet

ACOSOG Z1041[7,8]	Neoadjuvant chemotherapy • Arm A: FEC-75 ×4 → paclitaxel+ trastuzumab (q1w×12) • Arm B: paclitaxel + trastuzumab (q1w×12) → FEC-75 + trastuzumab ×4	282	HER2+, operable	Ongoing; 282 enrolled, pCR 56% (95% CI 48−65) in sequential arm, vs 54.2% (95% CI 46-63) in concurrent arm, OR=0.90 (95% CI 0·55−1·49). The most common severe adverse effects were neutropenia (25.3% sequential vs 31.7% concurrent) and fatigue (4.3% vs 8.5%)
GeparQuinto GBG 44[9,10]	Randomized to receive neoadjuvant trastuzumab or lapatinib: EC + trastuzumab (q3w×4)→T + trastuzumab (q3w×4) vs EC + lapatinib → T + lapatinib Pegfilgrastim administered with lapatinib as primary prophylaxis for febrile neutropenia and with trastuzumab as secondary prophylaxis	620	HER2+, ≥2 cm by palpation or ≥1 cm by sonography; cT1−4, 83% operable, 17% LABC, 31% CN0, 55% HR+	• 30.3% EC + trastuzumab→T + trastuzumab and 22.7% EC+ lapatinib→T + lapatinib group had pCR (OR=0.68, p=0.04) • Trastuzumab associated with more edema (39.1% vs 28.7%) and dyspnea (29.6% vs 21.4%) and less diarrhea and skin rash • Still ongoing, no long-term data
NeoSphere[11] NCT00545688	A. trastuzumab + docetaxel B. Pertuzumab + trastuzumab + docetaxel C. Pertuzumab + trastuzumab D. Pertuzumab + docetaxel All administered for 4 cycles neoadjuvant	417	HER2+; stratified by operable, locally advanced, and inflammatory, and by hormone receptor expression	B vs A, pCR 45.8% vs 29% D vs C, pCR 24.0% vs 16.8% Grade 3 neutropenia and leucopenia similar in Groups A, B, D; almost zero in group C Serious adverse events similar in A, B, D; lower in C Small study will not measure survival effects

Study	Trial arms	N	Characteristics	Outcome
JBCRG-10[12,13] [abstract]	Neoadjuvant chemotherapy 1. FEC ×4→TCH ×4 2. TCH ×4→FEC ×4 3. TCH ×6	180 planned ; 103 actual	HER2+, T1C-3, N0−1, M0	FEC arms were discontinued after interim analysis and there was insufficient power for conclusions on preferable sequence; decrease in LVEF was significant for FEC→TCH arm
ADAPT HER2+/HR+[14]	Neoadjuvant therapy (12 w) T-DM1 vs T-DM1 + endocrine therapy vs trastuzumab + endocrine therapy	380 planned	HER2+ HR+	Ongoing
ADAPT HER2+/HR−[14]	Neoadjuvant therapy (12 w) Trastuzumab + pertuzumab vs trastuzumab + pertuzumab + paclitaxel	220 planned	HER2+ HR−	Ongoing
Trastuzumab for <1 y				
FinHer[15,16]	3 cycles docetaxel or vinorelbine • HER2+ secondary randomization to trastuzumab or not for 9 w administered together with docetaxel or vinorelbine FEC administered after docetaxel/vinorelbine ± trastuzumab was complete	232	1010 pts overall, 232 HER2+ N+ or high-risk N0 (tumour diameter >20 mm, and PR−)	Median follow-up 62 mo, DDFS and OS rates: • Docetaxel better than vinorelbine overall, DDFS HR=0.66, p=0.010; OS HR=0.70, p=0.086 • HER2+: trastuzumab better than chemotherapy alone, DDFS HR=0.65 (95% CI 0.38−1.12), p=0.12; OS HR=0.55, p=0.094 • HER2+, adjusted for nodal metastases: DDFS HR=0.57, p=0.047 • Docetaxel + trastuzumab + FEC better than docetaxel + FEC (DDFS HR=0.32, p=0.29; OS HR=0.42, p=0.14) and vinorelbine + trastuzumab + FEC (DDFS HR=0.31, p=0.20) • Trastuzumab group had less heart failure (0.9% vs 1.7%) and change in median LVEF (0% vs 4% decrease) • Subgroup with very high HER2 content (≥22−fold the median of HER2− cancers) did not benefit from trastuzumab (HR=1.23, p=0.75) whereas the rest of the HER2+ pts did (HR=0.52, p=0.05)
PHARE[17-19] NCT00381901 2006−2010	6 mo vs 12 mo trastuzumab	3382	HER2+, early, at least 4 cycles (neo)adjuvant chemotherapy; median 2 cm, 45% N+, 58% ER+, 88% RT, 58% trastuzumab, 73% anthracycline and taxane containing chemotherapy	• Median follow-up 42.5 mo • DFS HR=1.28 (1.05−1.56), non-inferiority of 6 mo vs 12 mo could not be demonstrated because the 95% CI crossed the prespecified non-inferiority margin of 1.15 • Results inconclusive but trend in favour of 12 mo overall; subgroup analysis not yet complete • Higher cardiotoxicity in 12 mo group (5.7% vs 1.9%)
E-2198[20] NCT00003992 [abstract]	Arm A: Paclitaxel + trastuzumab (q3w×4)→AC Arm B: same regimen + trastuzumab for 52 w	234	HER2+, Stage II	Median follow-up 64 mo DFS equivalent for arms B and A (73% vs 76%, p=0.55) Congestive heart failure rate same (Arm B, N=4; Arm A, N=3)
PERSEPHONE[21]	6 vs 12 mo trastuzumab	Planned	HER2+, early	Ongoing

Study	Trial arms	N	Characteristics	Outcome
[abstracts]	Test for non-inferiority of 6 mo treatment	4000; 3080 to date		Recruitment expected to be completed late 2015 and first interim analysis mid-2016
Trastuzumab for 1 or 2 y				
HERA[22-24] BIG 1−01 2001−2005	Trastuzumab for 1 and 2 y (not reported) vs observation; all groups after standard neoadjuvant, adjuvant chemotherapy or both After 1 y, the control group was allowed to cross-over to trastuzumab and 52% did	3401	HER2+, early, 50% HR+, 33% N0 Inclusion criteria was N+ or N0 if >1 cm For N0: 60 pts <1 cm 33 pts 1 cm 510 pts >1 cm and <2 cm 484 pts ≥2 cm 566 pts HR− N0 533 pts HR+ N0 68% anthracyclines, 26% anthracycline + taxane 6% no anthracycline	Median follow-up 48.4 mo, 4−y survival rate results, trastuzumab vs control Intention-to-treat analysis: • DFS: 78.6% vs 72.2%, HR=0.76 (95% CI 0.66−0.87), p<0.0001 • OS: 89.3% vs 87.7%, HR=0.85 (95% CI 0.70−1.04), p=0.11 Censored for crossover • DFS 78.6% vs 71.7%, HR=0.69, p<0.0001 • OS 89.3% vs 81.5%, HR=53 (95% CI 0.44−0.65), p<0.0001 Crossover pts vs control • Fewer DFS events: HR=0.68 (95% CI 0.51−0.90), p=0.0077 More grade 3−4 (14% vs 8%) and fatal adverse events (1% vs 0.5%) on trastuzumab than observation 3-y DFS (1 y trastuzumab vs observation): N0 (all sizes): 90.8% vs 84.9%, HR=0.59 (95% CI 0.39−0.91) N0 (1.1−2 cm): 91.3% vs 86.7%, HR=0.53 (95% CI 0.26−1.07) N+ (N1): 84.7% vs 75.9%, HR=0.61 (95% CI 0.43−0.87) N+ (N2+): 67.8% vs 62.2%, HR=0.64 (95% CI 0.49−0.83) HR− N0: 87.1% vs 86.5%, HR=0.68 (95% CI 0.40−1.16) HR+ N0: 94.8% vs 83.4%, HR=0.46 (95% CI 0.23−0.93) 2-y DFS (1 y trastuzumab vs observation) N0: HR=0.59 (95% CI 0.39−0.91) N1: HR=0.61 (95% CI 0.43−0.87) N2: HR=0.64 (95% CI 0.49−0.83) T1 (0−2 cm): HR=0.65 (95% CI 0.47−0.90) T2 (>2−5 cm): HR=0.55 (95% CI 0.43−0.71)
HERA[25]	See previous entry in table	5102	Included landmark analysis of 3105 pts (2 vs 1 y trastuzumab) disease-free 1 y after randomization to trastuzumab	Median follow-up 8 y • DFS: 23.6% in both 2−y and 1−y group, HR=0.99 (95% CI 0.85−1.14), p=0.86 • DFS: 1 y vs observation, HR=0.76 (95% CI 0.67−0.86), p<0.0001) • OS: 1 y vs observation, HR=0.76 (95% CI 0.65−0.88), p=0.0005 despite crossover of 52% of pts from observation to trastuzumab

Study	Trial arms	N	Characteristics	Outcome
				• More pts had grade 3−4 adverse events in the 2 y group than 1 y group (20.4% vs 16.3%) or observation (8.2%). Included neoplasms, infections; nervous system, vascular, cardiac, musculoskeletal, gastrointestinal disorders (no significance values stated for these) • Conclude 2 y trastuzumab is not more effective than 1 y; 1 y remains standard of care
HERA, BIG 1−01[26]	See previous entry in table	5102		Median follow-up 8 y • Cardiac adverse events leading to discontinuation of trastuzumab 9.4% in 2−y arm and 5.2% in 1−y arm • 2 y vs 1 y vs observation: Severe congestive heart failure rate (0.8%, 0.8%, 0.0%) and confirmed significant LVEF decrease (7.2%, 4.1%, 0.9%) were significantly greater in both trastuzumab arms compared with controls • Acute recovery reached in 87.5% receiving 2−y trastuzumab and 81.2% of pts with 1−y trastuzumab
HERA[27]	See previous entry in table 1 y trastuzumab vs observation	3401		Competing risks analysis of cumulative incidence of first DFS events in the CNS vs other sites after median follow-up 4 y: CNS as first relapse 2% trastuzumab vs 2% control, p=0.55
Lapatinib (± trastuzumab) for 1 y				

TEACH[28-30]	Lapatinib (1500 mg) vs placebo daily for 12 m	3147	HER2+, previous adjuvant chemotherapy	Median follow-up 48 mo, lapatinib vs placebo:
				• DFS 87% vs 83%, HR=0.83 (95% CI 0.70−1.00), p=0.053
				• OS 94% vs 94%, HR=0.99 (95% CI 0.74−1.31), p=0.96
				• HR− pts: DFS 87% vs 80%, HR=0.68 (95% CI 0.52−0.89), p=0.006
				  • N0 subgroup: HR=0.57 (95% CI 0.35−0.92)
				  • N+ subgroup: HR=0.74 (95% CI 0.53−1.03)
				  • Premenopausal HR=0.59 (95% CI 0.37−0.94)
				• HR+ pts: DFS HR=0.98 (95% CI 0.77−1.25), p=0.89
				• Central review as HER2+ (79% of pts): DFS 87% lapatinib vs 83% placebo, HR=0.82 (95% CI 0.67−1.00), p=0.04
				• HER2− or borderline by central FISH testing: DFS 85% vs 81%, HR=0.94 (95% CI 0.56−1.57)
				More serious grade 3/4 adverse events with lapatinib than placebo (6% vs 5%): diarrhea 6% vs 0.6%, rash 5% vs 0.2%, hepatobiliary disorders 2% vs 0.1%
				Any adverse effect: diarrhea 61% vs 16% (p<0.0001), rash 59% vs 15% (p<0.0001), hepatobiliary disorders 8% vs 3% (p=0.21)

Study	Trial arms	N	Characteristics	Outcome
ALTTO BIG 2−06 NCCTG N063D[31,32] [abstract]	Lapatinib +trastuzumab (52 w) vs trastuzumab (12w) → lapatinib (34 w after 6 w delay) vs lapatinib (52 w) vs trastuzumab (52 w) • N=4613 after chemotherapy • N=3337 concurrent with anthracycline → taxane • N=431 concurrent with platinum-containing regimen	8381	Recruitment June 2007 to July 2011, L arm closed Aug 2011 for futility 40% N0, 57% HR+	Median follow-up 4.5 y, 4−y DFS Lapatinib + trastuzumab vs trastuzumab: 88% vs 86%, HR=0.84 (95% CI 0.70−1.02), p=0.048 Trastuzumab → lapatinib vs trastuzumab: 87% vs 86%, HR=0.93 (95% CI 0.76−1.13), p=0.044 both not significant at author's cut-off of p=0.025 Diarrhea (75% vs 20%), rash (55% vs 20%), hepatobilliary adverse effects (23% vs 16%) were more frequent in lapatinib + trastuzumab vs trastuzumab Primary cardiac endpoints <1% in all arms Quality of life substudy (N=777): worse in all arms at 12 w but returned to baseline by end of treatment at 52 w Follow-up continues
Trastuzumab for 1 y				
NSABP B31 and NCCTG N9831 combined analysis[33] 2000−2005	AC→ paclitaxel ± trastuzumab N9831 Arms A and C, NSABP B31 Groups 1 and 2, see later in this table	4045	See later in this table	Median follow-up 3.9 y, significant improvement favouring trastuzumab • DFS: HR=0.52 (95% CI 0.45−0.60), p<0.001 • OS: 39% reduction, HR=0.61 (95% CI 0.50−0.75), p<0.001 Analyzed by nodal status, significant only for N+ • 0 nodes: 4-y DFS 86.8% vs 89.6%, events HR=1.78 (95% CI 0.3−10.7) (not significant, only 33 events occurred) • 1−3: DFS 89.7% vs 80.6%, HR=0.58 (95% CI 0.40−0.82) • 4−9: DFS 83.5% vs 71.1%, HR=0.68 (95% CI 0.48−0.98) • 10+: DFS 73.7% vs 46.5%, HR=0.55 (95% CI 0.38−0.81) Effective for all tumour sizes 0−2 cm: DFS 90.9% vs 81.6%, HR=0.39 (95% CI 0.26−0.60) 2.1−5 cm: DFS 83.2 vs 70.3%, HR=0.72 (95% CI 0.55−0.94) >5 cm: DFS 78.2% vs 52%, HR=0.61 (95% CI 0.35−1.06) Effect was similar for all tumour grades, and both HR+ and HR−
NCCTG N9831[34-39] 2000−2005	• Arm A: AC (q3w×4) → paclitaxel (q1w×12) • Arm, B (sequential): AC → paclitaxel → trastuzumab (q1wx52) • Arm C (concurrent): AC → paclitaxel + trastuzumab (q1w×12) → trastuzumab (q1w×4)	3505	HER2+, operable, Stage I-III, N+ or high-risk N0 39% <2 cm 51% between 2.1−4.9 cm 8% ≥5 cm 13% N0 Initially only N+ disease; as of May 2, 2003, pts	• Median follow-up 6 y, 5−y results[34] • Arm B vs A: DFS 80.1% vs 71.8%, HR=0.69 (95% CI 0.57−0.85), p<0.001; OS: 89.3% vs 88.4%, HR=0.88 (95% CI 0.67−1.15), p=0.343 • Arm C vs B: DFS 84.4% vs 80.1%, HR=0.77 (95% CI 0.53−1.11) • Trend toward increase in DFS with C compared with B (concurrent vs sequential), but not significant because the p value (0.02) did not cross the prespecified O'Brien-Fleming

Study	Trial arms	N	Characteristics	Outcome
	RT or hormonal therapy after completion of chemotherapy when indicated		with high-risk N0 (>2 cm +HR+; or >1 cm and HR−)	boundary (0.00116) for the interim analysis • Cardiac events (congestive heart failure or cardiac death): 3−y cumulative incidence 0.3%, 2.8%, 3.3% in Arms A, B, C, respectively; cardiac function improved following trastuzumab discontinuation and cardiac medication[35] • Did not find association between MYC amplification and additional trastuzumab benefit[37] • Trastuzumab benefit seemed independent of HER2 centromere 17 ratio and chromosome 17 copy number[38] • Both HR+ and HR− pts benefit from trastuzumab (HR=0.42, p=0.005 and HR=0.60, p=0.0001)[38]
NSABP B-31[33,40] 2000−2005	AC (q3w×4) → paclitaxel (q3w×4 or q1w×12) vs AC → paclitaxel + trastuzumab (P=q3w×4 or q1w×12; H=q1wx52)	2101	HER2+, operable, N+	See joint analysis with NCCTG N9831 previous entry in table Cardiac function assessment at 7−y follow-up • Cardiac events: 4.0% trastuzumab vs 1.3% control; RR=3.30 (95% CI 1.63−6.66), p<0.001 • One cardiac death in each arm • Most pts recovered LVEF in the normal range after stopping trastuzumab, although some decline from baseline often persists
BCIRG 006, UCLA-0102006[41,42] 2001−2004	• [AC → TH]: AC q3w×4 → T q3w×4, trastuzumab q1w during chemotherapy then q3w until 1 y • TCH: Docetaxel + carboplatin (q3w×6) + trastuzumab (q1w during chemotherapy then q3w until 1 y • AC→T: AC q3w×4 → T q3w×4	3222	HER2+, early T1−3, N0−1, M0; N+ or high risk N0 (N=922); for N0 (assessed by SLNB or at least 6 nodes resected) at least one risk factor of age ≤35 y, tumour >2 cm, HR−, histological and/or nuclear grade 2/3 29% N0, 38% N1, 23% N2, 10% N3 40% T1 (≤2 cm), 53% 2−5 cm	Median follow-up 65 mo • AC → TH vs AC → T • DFS: 84% vs 75%, HR=0.64, p<0.001 • N0: 93% vs 85%, HR=0.47 (95% CI 0.28−0.77), p=0.0028 • N+ : 80% vs 71%, HR=0.68 (95% CI 0.56−0.84), p=0.0003 • N+ (≥4 nodes): HR=0.66 (95% CI 0.51−0.86), p=0.0017 • Tumour size <1 cm: HR=0.36 (95% CI 0.14−0.93), p=0.034 • Tumour size <2 cm: HR=0.73 (95% CI 0.49−1.09) • Tumour size ≥2 cm: HR=0.62 (95% CI 0.50−0.76), p<0.0001 • OS: 92% vs 87%, HR=0.63, p<0.001 • N0: HR=0.38 (95% CI 0.17−0.87) • N+: HR=0.67 (95% CI 0.50−0.88) • Tumour size <2 cm: HR=0.49 (95% CI 0.27−0.91) • Tumour size ≥2 cm: HR=0.66 (95% CI 0.49−0.88) • TCH vs AC → T • DFS: 81% vs 75%, HR=0.75, p=0.04 • N0: 90% vs 85%, HR=0.64 (95% CI 0.41−1.01), p=0.057

Study	Trial arms	N	Characteristics	Outcome
				• N+: 78% vs 71%, HR=0.78 (95% CI 0.64−0.95), p=0.013 • N+ (≥4 nodes): HR=0.66 (95% CI 0.51−0.86), p=0.0016 • Tumour size <1 cm: HR=0.45 (95% CI 0.17−1.16), p=0.096 • Tumour size <2 cm: HR=1.11 (95% CI 0.73−1.69), p=0.64 • Tumour size ≥2 cm: HR=0.70 (95% CI 0.57−0.87), p=0.0009 • OS: 91% vs 87%, HR=0.77, p=0.04 • N0: HR=0.56 (95% CI 0.27−1.13) • N+: HR=0.81 (95% CI 0.62−1.05) • Tumour size <2 cm: HR=0.75 (95% CI 0.43−1.29) • Tumour size ≥2 cm: 0.77 (95% CI 0.58−1.02) • No significant difference in OS or DFS among trastuzumab regimens, but both superior to AC→T (AC→TH stronger effect in some subgroups) • Benefit in N0, N+, and high risk N+ (≥4 positive nodes) • Without TOP2A co-amplification: DFS benefit with trastuzumab even larger, but trastuzumab had no DFS benefit in TOP2A co-amplified (but TCH still better therapeutic index because of adverse effects profile) • Congestive heart failure and cardiac dysfunction higher in AC→T + trastuzumab than TCH (p<0.001) • 7 acute leukemia in AC-based regimens vs 1 in TCH group (but received anthracycline outside the study)
BCIRG 006[43]	See previous entry in table	3222		Health-Related Quality of Life questionnaire, assessed at baseline (all groups similar), midpoint (cycle 4), end of chemotherapy, 12-mo follow-up: • Physical scale, global health, and systemic effects deteriorated for all groups but recovered by 12 mo • Repeated measurement analysis found significantly better physical, global health, and less systemic effects with TCH
FNCLCC PACS-04[44]	FEC or epirubicin/docetaxel; HER2+ secondary randomization to trastuzumab for 1 y or observation	3010	3010 pts overall, N+; 528 in HER2+ subgroup	Median follow-up 47 mo 14% reduction in risk of relapse with trastuzumab, HR=0.86 (95% CI 0.61−1.22), p=0.41 3−y DFS: 81% vs 78%, HR=0.86 (95% CI 0.61−1.22) OS: 95% vs 96%, HR=1.27 (95% CI 0.68−2.38) Of trastuzumab group, 10% did not receive trastuzumab and 18% discontinued trastuzumab before 6 mo due to cardiac events or progressive disease

Study	Trial arms	N	Characteristics	Outcome
N-SAS BC 07 RESPECT[45]	Trastuzumab monotherapy for 1 y vs trastuzumab + chemotherapy	300 planned	HER2+, Age >70 y, Stage I, IIA, IIB, IIIA/M0	Protocol only
Trastuzumab in HER2 low pts (IHC 1+ or 2+)				
NSABP B-47[46]	Chemotherapy ± 1 y of trastuzumab Chemotherapy by physician choice, either TC (q3w×6) or AC (q3w×4 or q2w×4)) plus paclitaxel (q1w×12)	3260 planned	HER2 IHC 1+ or 2+ scores but non-amplified by FISH N+ or high-risk N0	Ongoing 1416 enrolled Feb 2011−Jan 2013
Second agent (pertuzumab or neratinib) after trastuzumab				
ExteNET, NCT00878709[47]	Neratinib for 1 y vs placebo	2842	HER2+, N+ pts who completed adjuvant trastuzumab within 1 y before randomization	No results released yet, recruitment completed 2012, see http://clinicaltrials.gov/show/NCT00878709
APHINITY BIG 4−11 NCT01358877[48]	1 y trastuzumab + pertuzumab vs trastuzumab Chemotherapy is investigator's choice between anthracycline-taxane or taxane-platin containing regimens	4800	HER2+ with excision of tumour and adjuvant chemotherapy; either • N+ (pN1), • N0 and T>1cm, • or N0 and T 0.5−1 cm and one of grade 3, ER−/PR−, age <35 y Randomized 3−7 w after surgery	Ongoing Accrual complete August 2013[49]

Abbreviations: AC; doxorubicin + cyclophosphamide; DDFS, distant disease-free survival; DFS, disease-free survival; EC, epirubicin + cyclophosphamide; ER, estrogen receptor; FEC, fluorouracil + epirubicin + cyclophosphamide; HER2, human epidermal growth factor receptor 2; HR-, hormone receptor negative; HR+, hormone receptor positive; LVEF, left ventricular ejection fraction; LABC, locally-advanced breast cancer; N+, node-positive; N0, node-negative; OS, overall survival; pCR, pathologically complete response; RT, radiation therapy; TCH, docetaxel + carboplatin + trastuzumab; T, docetaxel; T-DM1, trastuzumab emtansine; TH, docetaxel + trastuzumab.

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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