A Summary of the GATE Appraisals of the Trastuzumab trials

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Background

In May 2007, PHARMAC commissioned Dr. Susan Wells, Senior Lecturer in Clinical Epidemiology at Section of Epidemiology and Biostatistics, University of Auckland to independently critically appraise using the GATE tool, the five relevant clinical trials (HERA, B31, N9831, BCIRG006, and FinHer) assessing the impact of the drug trastuzumab used for breast cancer.

The Graphic Appraisal Tool for Epidemiology (GATE) frame[1] is a visual framework designed for critical appraisal developed by Rod Jackson and colleagues (including Dr Wells), emerging and developing from the Evidence-Based Medicine (EBM) Working Group Users' Guides[2] to the Medical Literature (the 28-article series published in JAMA by Sackett, Oxman, Guyatt et al.). The framework graphically represents the generic structure of all epidemiological studies and substantively helps systematise critical appraisal in a comprehensive but intuitive way. Details on the GATE framework are available at the EPIQ website (www.epiq.co.nz) and the EBM article[1].

This work was not intended to integrate the epidemiological evidence with patient preferences, policy issues or clinical considerations (page 4 of GATE) nor provide a meta-analysis or other formal policy document.
The GATE appraisals for the five studies are attached as an Appendix.

Acknowledgements

The reviewer thanks Prof Anthony Rodgers (Epidemiologist, Clinical Trials Research Unit, School of Population Health) and Prof Vernon Harvey (Specialist Oncologist, Auckland Hospital) for sharing their expertise and their time in discussions on aspects of the trials as part of the appraisal process.

[1] Jackson R, Ameratunga S, Broad J, Connor J, Glasziou P, Heneghan C, Lethaby A, Robb G, Wells S. The GATE frame: critical appraisal with pictures. *Evidence Based Medicine* 2006;11:35-38. Also published in: *ACP Journal Club* for March/April 2006;144(2) A8-11; and in: *Evidence Based Nursing* 2006;9: 68-71.

[2] The User Guides series published by JAMA is available at http://www.cche.net/userguides/main.asp

Summary of GATE Appraisal of Trastuzumab Trials

Trastuzumab is a monoclonal antibody against human epidermal growth receptor 2 protein (HER2). Overexpression of the HER2 protein, amplification of the HER2 gene, or both, occur in approximately 15-25% of breast cancers and are associated with aggressive behaviour in the tumour[1]. Hence the hypothesis that for women with breast cancer who have an overexpression of HER2, trastuzumab might be useful as adjuvant therapy (before/after/in combination) with established other chemotherapeutic agents (eg anthracyclines and taxanes), surgery and radiation treatment.

The reviewer has been asked by Pharmac to independently critically appraise (using the GATE tool) randomised controlled trials of the drug trastuzumab used for breast cancer. The following randomised trials have been published to date, reporting outcomes for adjuvant trastuzumab against standard treatment in early stage (non–metastatic) HER2 +ve invasive breast cancer. They investigate three broad regimens :-

1) **Sequential (post anthracyclines +/- taxanes)-** trastuzumab for 12 months following completion of chemotherapy.

- The Herceptin Adjuvant (HERA) Trial with one year (Piccart-Gebhert M.J. et al. 2005) and 2-year follow-up (Smith I. et al. 2007)

2) **Concurrent post anthracycline chemotherapy-** trastuzumab for 12 months started in combination with a taxane following completion of anthracyclines.

- The joint results of National Surgical Adjuvant Breast and Bowel Project trial B-31 (NASBP B31) and NCCTG N9831 reported by Romond E.H. et al. 2005 with further results of NCCTG N9831analyses available as slide presentation only by Perez E et al. at the 2005 ASCO annual meeting.
- BCIRG trial available as slide presentation only by Salmon D. et al. at the 2006 ASCO annual meeting.

3) **Concurrent pre- anthracycline chemotherapy-** trastuzumab for 9-10 weeks started in combination with a taxane prior to anthracycline chemotherapy.

- The FinHer Study (Joensuu H. et al. 2006).

The following pages contain summaries (“GATE- Lite”) of each of the studies with the full GATE appraisal available as separate Excel spreadsheet workbooks in the Appendix. Comments on the overall study quality and degree of variation in quality over epidemiological study design key domains are given at the end of each study summary.

[1] Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2neu oncogene. Science 1987; 235:177-82

General statement on the overall quality of the studies appraised:

- All are stratified randomised trials. However with the exception of FinHer allocation concealment is not reported. Inadequate or unclear allocation concealment has been associated with 30-40% larger estimates of treatment effects. [1]

- The trials appear to have enrolled women with early invasive breast cancer with similar prognostic characteristics in terms of age, axillary nodal status although the definition of "high risk" node-negative (HERA, BCIRG, FinHer, N9831) is not clearly reported in some of the publications (BCIRG). Other important prognostic factors such as mastectomy, radiotherapy, hormonal therapy, tumour size, hormone receptor status, menopausal status and cardiovascular risk factors are variably reported.

- All studies are unblinded and outcomes were also assessed unblinded. Possible direction of bias for this is lowering of treatment effect due to co-intervention. In other words, if clinicians in the study considered trastuzumab to be an effective drug there would be a greater likelihood of more aggressive chemotherapy/hormonal therapy for those known to be in the control group.

- The outcomes were fairly objective (disease free survival and overall survival) therefore non-blinded outcome assessment may not have a large impact. However if trastuzumab was known to cause cardiac toxicity this may lead to an overestimate of adverse cardiac outcomes (particularly decline in LVEF).

- Outcomes of interest that are not addressed in any study are longer term effects of tratsuzumab on cardiac toxicity and overall survival, differences in quality of life and return to usual daily activities.

- Most represent interim analyses; none have met their preset event accrual rates required in the power calculations given although some studies are large enough to demonstrate clinically significant and statistically precise results.

- There is variable reporting of compliance, contamination and co-intervention.

- Follow up is good and analyses are mainly according to Intention to Treat principle.

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[1] Schulz K F. Assessing allocation concealment and blinding in randomised controlled trials. Why bother? *Evidence Based Medicine* 2000; 5:36-37

- Assessment of quality of B31 and N9831 is less than ideal as reporting is limited to either the published joint analysis (Romond 2005) for B31 and N9831 arms A and C with little description of some of the key validity aspects of the separate studies. There is even more limited reporting of N9831 arms A, B and C within the Perez conference slideshow presentation.

- Unable to assess the quality of BCIRG006 because reporting is limited to conference slideshow presentation.

- In terms of disease free survival, all of the trials favour treatment with adjuvant trastuzumab over control chemotherapy whether the regimen was sequential or concurrent (pre or post anthracyclines) and whether the trastuzumab course was 9 weeks or one year.

- Only Smith et al.(HERA), Romond et al (joint analysis B-31 and N9831) and Salmon et al. (BCIRG) have been able to show significant differences in overall survival and used a one year regimen with trastuzumab. Other publications (HERA 2005, Perez N9831, FinHer) are either underpowered or the follow-up time is too short to detect significant differences in overall survival.

Additional comments from Oncologist review

- In the past, cancer chemotherapy was delivered via regimens of longer duration (eg, up to one year). These regimens have shortened considerably due to evidence of benefits outweighing harms.
- There has been early separation of survival curves seen with the trials of trastuzumab compared with control chemotherapy, regardless of the regimens used.
- There is a pressing need to formally test in a randomised control trial the effectiveness of a one year trastuzumab (post anthracycline) regimen compared with 9 or 10 week trastuzumab (pre-anthracycline) regimen.

Individual Trial Summaries

Piccart-Gebhart M.J. et al (2005) for the HERA trial study team.

Regimen = Sequential (post anthracyclines +/- taxanes)- trastuzumab for 12 months following completion of chemotherapy.

Study	**Piccart-Gebhart M.J. et al (2005) for the HERA trial study team.**
Participants	3387 women enrolled between Dec 2001 and March 2005 from 478 participating institutions in 39 countries with HER2 positive completely excised invasive breast cancer, node positive or negative who had completed surgery +/- DXT and a minimum of 4 cycles of approved chemotherapy regimens(post-op, pre-op or both) AND normal LVEF post chemotherapy.
Exposure	Trastuzumab given at dose of 8mg/kg i.v. as a 90 minute infusion loading dose followed by 6mg/kg every 3 weeks for one year (n=1674)
Comparison	Observation (n=1693)
Outcomes	**Primary outcome**: disease free survival **Secondary outcomes:** cardiac safety, overall survival, site of 1st disease-free survival event, time to distant recurrence
Time	one year median follow-up (range 0-36 months)
Results: RR	Disease free survival RR 0.54 (0.43-0.67) Overall survival RR 0.76 (0.47-1.23) *Harms* Serious adverse effects GATE RR 1.44 (1.1-1.9) Symptomatic CHF GATE RR 28.98 (3.95-212.52)
Results: RD	8.4% (2.1-14.8) absolute benefit disease free survival at 2 years (NNT 18) 0% (-1.0 to 0%) absolute benefit in overall survival *Harms* 2% (1.0 -2.0) absolute increase in serious adverse effects (NNT 48) 2% (1.0-4.0) absolute increase in Symptomatic CHF (NNT 61)
Validity	
Representativeness	95% white or asian women (less than 5% black or other), 75% between 35-59 years, unknown smoking and socioeconomic status and treated in secondary care settings with surgical, radiation, cardiac imaging, pathology and other services available. It is not reported how participants were selected from the eligible population, nor what % of eligible women actually consented to take part.
Allocation	Stratified randomisation but allocation concealment not reported
Adjustment	Exp and comp group factors well-balanced –no adjustment in analyses.
Maintained- blind?	Open label- unblinded

Compliance	Not reported percentage compliance with full therapy, 1% did not receive treatment, 8.4% withdrew from treatment
Contamination	Low (0.1%)
Co-intervention	Not reported
Follow-up	All followed up
Blind/Objective outcome measurement	Outcome assessment unblinded.Reasonably objective primary endpoint. The cardiac secondary endpoints included multiple modes of asessment. Echos and MUGA scan results were reviewed by "core" staff, however no measures of reliability (inter-rater) were given.
ITT analyses	ITT was conducted for primary endpoints including those who violated eligibility criteria, but not for safety analyses

Comments on key validity domains

Whilst the study was randomised, allocation concealment was not reported. Inadequate or unclear allocation concealment have been associated with 30-40% larger estimates of treatment effects.
The study was unblinded and outcomes were also assessed unblinded. Possible direction of bias for this is lowering of treatment effect due to co-intervention or more aggressive chemotherapy/hormonal therapy for those known to be in the control group (especially if clinicians in the study considered trastuzumab to be an effective drug). The outcomes were fairly objective (disease free survival and overall survival) therefore non-blinded outcome assessment may not have a large impact. However if trastuzumab was known to cause cardiac toxicity this may lead to an overestimate of adverse cardiac outcomes particularly estimation of changes in LVEF rather than symptomatic CHF.
ITT was conducted for the primary endpoint and the effect estimate for disease free survival was precise with a NNT 18. Very consistent relative benefits were noted across all subgroups (around 50% RRR). The GATE estimated NNT(H)=48 for serious adverse effects of trastuzumab and NNT(H)=61 for development of symptomatic CHF.

Overall Study Quality

Reasonable quality however this was an interim analysis with follow-up too short to determine overall survival benefit.
Other patient outcomes not assessed were longer term effects of cardiac toxicity , differences in quality of life and return to usual daily activities.

Smith I. Et al. (2007) for the HERA trial study team.

Regimen = Sequential (post anthracyclines +/- taxanes)- trastuzumab for 12 months following completion of chemotherapy.

Study	**Smith I. Et al. (2007) for the HERA trial study team.**
Participants	3401 women (enrolled between Dec 2001 and June 2005 from 478 participating institutions in 39 countries) with HER2 positive completely excised invasive breast cancer, node positive or negative who had completed surgery +/- DXT and a minimum of 4 cycles of approved chemotherapy regimens(post-op, pre-op or both) AND normal LVEF post chemotherapy.
Exposure	Trastuzumab given at dose of 8mg/kg i.v. via 90 minute infusion loading dose followed by 6mg/kg every 3 weeks for one year (n=1703)
Comparison	Observation (n=1698)
Outcomes	**Primary outcome**: Disease free survival **Secondary outcomes:** cardiac safety, overall survival, site of 1st disease-free survival event, time to distant recurrence
Time	2 years (median follow-up 23.5 months with range 0-48 months)
Results: RR	Disease free survival RR 0.64 (0.54-0.76) Overall survival RR 0.66 (0.47-0.91) *Harms* Serious adverse effects GATE RR 1.6 (1.26-2.05) Symptomatic CHF GATE RR 17.95 (4.33-74.42)
Results: RD	6 % (4.0-9.0) absolute benefit Disease free survival at 3 years (NNT 16) 2% (0- 3.0) absolute benefit in overall survival (NNT 54) *Harms* 3% (2.0-5.0)absolute increase in serious adverse effects (NNT[H] 30) 2% (1.0-3.0) absolute increase in symptomatic CHF (NNT[H] 51)
Validity	
Representativeness	95% white or asian women (less than 5% black or other), 75% between 35-59 years, unknown smoking and socioeconomic status and treated in secondary care settings with surgical, radiation, cardiac imaging, pathology and other services available. It is not reported how participants were selected from the eligible population, nor what % of eligible women actually consented to take part.
Allocation	Stratified randomisation but allocation concealment not reported
Adjustment	Exp and comp group factors well- balanced –no adjustment in analyses.
Maintained- blind?	Open label- unblinded
Compliance	Not reported percentage compliance with full therapy, 1% did not receive trastuzumab, 10.1% withdrew from Rx
Contamination	High -861/1698 (51%) women switched from observation to trastuzumab.

Co-intervention	Not reported
Follow-up	155/3401 (4.6%) were lost to follow-up; 97 (5.7%) from observation group and 58 (3.4%) from trastuzumab group.
Blind/Objective outcome measurement	Outcome assessment unblinded.Reasonably objective primary endpoint. The cardiac secondary endpoints included multiple modes of asessment. Echos and MUGA scan results were reviewed by "core" staff, however no measures of reliability (inter-rater) were given.
ITT analyses	ITT was conducted for primary endpoints including those who violated eligibility criteria, but not for safety analyses AND they also did not include 271/861 patients who after moving to trastuzumab developed an adverse event.

Comments on key validity domains

Whilst the study was randomised, allocation concealment was not reported. Inadequate or unclear allocation concealment have been associated with 30-40% larger estimates of treatment effects in some trials.
The study was unblinded and outcomes were also assessed unblinded. Possible direction of bias for this is lowering of treatment effect due to co-intervention or more aggressive chemotherapy/hormonal therapy for those known to be in the control group (especially if clinicians in the study considered trastuzumab to be an effective drug). This is likely to be operating as it is reported that as of May 2006, 51% of women (861/1698) originally assigned to observation group had switched to trastuzumab.
Although disease free survival benefit was similar with both censored and ITT analysis this significant contamination will reduce the study's ability to address longer term outcomes and women switching over later will have differing follow-up time from the original trastuzumab group.
The outcomes were fairly objective (disease free survival and overall survival) therefore non-blinded outcome assessment may not have a large impact. However if trastuzumab was known to cause cardiac toxicity this may lead to an overestimate of adverse cardiac outcomes particularly estimation of changes in LVEF rather than symptomatic CHF.
.
ITT was conducted for the primary endpoint and the effect estimates for disease free survival were precise with a NNT 16 and consistent relative benefits noted across all subgroups (around 40% RRR).

Of note this study did show a 2% (0- 3.0) absolute benefit in Overall survival (NNT 54) after median 2yrs follow-up.

ITT was not conducted for safety analyses AND they also did not include 271/861 patients who after moving to trastuzumab developed an adverse event.
The GATE estimated NNT(H)=30 for serious adverse effects of trastuzumab and NNT(H)=51 for development of symptomatic CHF.

Overall Study Quality

A reasonably good study, large numbers, precise confidence intervals but some methodological issues. Study showed a significant reduction in disease free survival and

overall survival after median 2yrs follow-up with sequential (post anthracyclines +/- taxanes) trastuzumab for 12 months following completion of chemotherapy. Significant contamination is likely to influence future results.Other patient outcomes not assessed were longer term effects on cardiac status and survival, short term differences in quality of life and return to usual daily activities.

Romond et al (2005) The joint results National Surgical Adjuvant Breast and Bowel Project trial B-31 (NASBP trial B-31) & NCCTG trial N9831

Concurrent post anthracycline chemotherapy- trastuzumab for 12 months started in combination with a taxane following completion of anthracyclines.

Study	**Romond et al (2005) The joint results National Surgical Adjuvant Breast and Bowel Project trial B-31 (NASBP trial B-31) & NCCTG trial N9831**
Participants	3676 Women (attending at least 35 institutions from several states in America) with non-metastatic breast ca, HER2 3+/amplification, node positive disease or high risk node negative disease.Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. **NB** Slightly diff incl/excl criteria in 2 studies.
Exposure	**AC-TH** 4 cycles of Doxorubicin 60mg/m^2 BSA and cyclophosphamide 600mg/m^2 every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/m^2 every 3 weeks) plus trastuzumab 4mg/kg with 1st dose of paclitaxel followed by weekly infusions 2mg/kg for 51 weeks. **NB** slightly diff exp/comp regimens in 2 studies (n=1833)
Comparison	**AC-T** As above but no trastuzumab (n=1843)
Outcomes	**Primary outcome**: Disease-free survival **Secondary outcomes:** Overall survival, time to distant recurrence, death from breast cancer, contralateral breast cancer and other secondary primary cancers and adverse cardiac events
Time	Median follow-up 1.5 years
Results: RR	Disease free survival (combined studies) RR 0.48 (0.39-0.59) Overall survival RR 0.67 (0.43-0.93) *Harms* Adverse cardiac events GATE RR 10.46 (4.19-26.12)
Results: RD	7% (5.0-9.0) absolute benefit in disease free survival at median 1.5 yr (NNT14) 2% (0-3.0) absolute benefit in overall survival (NNT 62) *Harms* 3% (2.0-3.0) absolute increase in adverse cardiac events (NNT[H] 39)
Validity	
Representativeness	Poorly reported. The women were American, 2/3 between 40 and 60yrs, with the other 1/3 equally divided between those less than 40 and over 60yrs. They were of unknown ethnicity, smoking and socioeconomic status and presumed treated in secondary care/specialist cancer settings
Allocation	2 types of stratified randomisation with allocation concealment not reported
Adjustment	The groups from each study were similar. The combined exposure

	& comparison groups were also similar with the exception of 191 patients with node-negative cancer enrolled in N9831. Adjustments made for nodal status, tumour size , receptor status, age, tumour grade, histological findings & trial (B-31 or N9831)
Maintained- blind?	Open label- unblinded
Compliance	Most had all doxo/cyclo/paclitaxel but about 1/3 stopped trastuzumab before 52 weeks.
Contamination	Not reported
Co-intervention	Not reported
Follow-up	9% lost to follow-up
Blind/Objective outcome measurement	Outcome assessment unblinded. Primary endpoint well described and objective. The cardiac secondary endpoints included multiple asessment via MUGA (B-31) or either echocardiography or MUGA scanning (N9831) Not reported who did the scans, no measures of reliability given.
ITT analyses	No, not true ITT analysis \Women who declined initial Rx and were subsequently lost to follow-up were not included in the analyses.

Comments on key validity domains

The control groups of these 2 trials as well as the concurrent trastuzumab-paclitaxel exposure groups differed in terms of scheduling of paclitaxel treatment and some aspects of hormonal therapy, radiotherapy and cardiac outcome assessment but were otherwise very similar and NCI and FDA approved a joint analysis plan. Ideally however, both trials need to be reported separately to assess quality of each study as several areas relating to validity were not reported or poorly reported.

Whilst the study was randomised (albeit 2 differing types of stratified randomisation), allocation concealment was not reported. Inadequate or unclear allocation concealment have been associated with 30-40% larger estimates of treatment effects in some trials. The study was unblinded and outcomes were also assessed unblinded. Possible direction of bias for this is lowering of treatment effect due to co-intervention or more aggressive chemotherapy/hormonal therapy for those known to be in the control group (especially if clinicians in the study considered trastuzumab to be an effective drug).

About 1/3 stopped trastuzumab before 52 weeks which might also reduce the overall treatment effect. Contamination was not reported.
The outcomes were fairly objective (disease free survival and overall survival) therefore non-blinded outcome assessment may not have a large impact. However if trastuzumab was known to cause cardiac toxicity this may lead to an overestimate of adverse cardiac outcomes.

ITT was conducted for the primary endpoint and the effect estimates for disease free survival were precise with a RRR around 50% and NNT 14 after median 1.5 years of follow-up.

With this joint analysis a 2% (0-3.0) absolute benefit in overall survival (NNT 62) was shown.

True ITT not conducted but from our crude analyses the effect estimates are similar with on-treatment and ITT analyses.
The GATE estimated NNT(H)=39 for serious adverse cardiac events.

Overall Study Quality

Combined results from 2 separate trials improve the power of the studies to demonstrate an effect (especially for overall survival) whereas on their own they may not. Ideally however, both trials need to be reported separately to assess quality of each study as several areas relating to validity were not reported or poorly reported. Likely to be some bias from methodological issues but difficult to assess if they were sufficient to have an important effect on the outcome. These analyses show significant reductions in disease free survival and overall survival after median 1.5 yrs follow-up with concurrent post anthracycline chemotherapy (trastuzumab for 12 months started in combination with a taxane following completion of anthracyclines). This effect remains even after adjusting for nodal status, tumour size , receptor status, age, tumour grade, histological findings & trial.
Other patient outcomes not assessed were longer term effects on cardiac status and survival, short term differences in quality of life and return to usual daily activities. Unlike the HERA studies unanswered questions also relate to differing patient sub-groups.

Perez ASCO results from NCCTG N9831 trial follow-up to May 2005

Concurrent post anthracycline chemotherapy- trastuzumab for 12 months started in combination with a taxane following completion of anthracyclines.
AND
Sequential (post anthracyclines +/- taxanes)- trastuzumab for 12 months following completion of chemotherapy.

Study	**Perez ASCO results from NCCTG N9831 trial follow-up to May 2005**
Participants	Women from 17 institutions from several states in America enrolled Feb 2000-Feb 2005 with non-metastatic breast ca, HER2 3+/amplification, node positive disease or high risk node negative disease.Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal.
Exposure	**AC-TH**: 4 cycles of doxorubicin and cyclophosphamide followed by weekly paclitaxel for 12 weeks plus 52 weeks of trastuzumab beginning day 1 paclitaxel (**concurrent exp**=Group C n=840) **AC-T-H** same chemo plus 52 weeks of trastuzumab after completion of paclitaxel (**sequential exposure**=Group B n=985).
Comparison	**AC-T** 4 cycles of doxorubicin and cyclophosphamide followed by weekly paclitaxel for 12 weeks (**control**=Group A n=979);
Outcomes	**Primary outcome**: Disease-free survival **Secondary outcomes:** Overall survival, time to distant recurrence, death from breast cancer,contralateral breast cancer and other secondary primary cancers and adverse cardiac events
Time	Median follow-up 1.5 years
Results: RR	Disease free survival sequential vs control RR 0.87 (GATE RR 0.87; 0.68-1.12) Disease free survival concurrent vs control RR 0.43 (GATE RR 0.60; 0.05-0.72) Disease free survival concurrent vs sequential RR 0.64 (GATE RR 0.74; 0.53-1.03)
Results: RD	seqential vs control -1% (95% CI crosses null) absolute increase in disease free survival at median 1.5 year follow-up. concurrent vs control -11% (7-14%) absolute increase in disease free survival concurrent vs sequential -2% (95% CI crosses null) improvement in disease free survival *Harms* <4% difference reported in the incidence of cardiac events (CHF and cardiac deaths) between non-trastuzumab and trastuzumab arms
Validity	
Representativeness	Poorly reported (gleaned from Romond et al 2005). The women were American, 2/3 between 40 and 60yrs, with the other 1/3

	equally divided between those less than 40 and over 60yrs. They were of unknown ethnicity, smoking and socioeconomic status and presumed treated in secondary care/specialist cancer settings
Allocation	Stratified randomisation, allocation concealment not reported
Adjustment	As reported in Romond, the exp & comp groups were similar. Unknown if adjustments were made in these analyses
Maintained- blind?	Open label- unblinded
Compliance	As reported in Romond, the majority received most all doxo/cyclo/paclitaxel chemotherapy but about 1/3 stopped trastuzumab before 52 weeks.
Contamination	Not reported
Co-intervention	Not reported
Follow-up	9% lost to follow-up
Blind/Objective outcome measurement	Outcome assessment unblinded. Primary endpoint well described and objective. The cardiac secondary endpoints included multiple asessment via either echocardiography or MUGA scanning (N9831) Not reported who did the scans, no measures of reliability given.
ITT analyses	Unable to assess

Comments on key validity domains

Allocation concealment not reported.Unblinded outcome assessment, ITT not reported. Results indicate that concurrent compared to control treatment is significantly better in terms of disease free survival but not able to support benefit of sequential over control Rx . It must be remembered that there are differences in follow-up timing for sequential and concurrent groups that may affect the results; sequential in effect having less follow-up time; concurrent having started treatment earlier. As indicated in the powerpoint presentation, by the 9th month post randomisation, concurrent patients had received 3 additional months of trastuzumab compared to sequential.

Overall study quality

Difficult to assess due to limited data presented at conference slide show presentation and uncertainty around analyses and study quality areas even though some of this has been gleaned from Romond et al 2005. Although the study showed a significant difference between concurrent vs control treatment these are interim analyses conducted in too short follow-up time and the study has not yet met preset target event accruals rates needed.

Salmon et al.2006 BCIRG 006

Concurrent post anthracycline chemotherapy- trastuzumab for 12 months started in combination with a taxane+/- caboplatin following completion of anthracyclines.

Study	**Salmon et al. Slide show BCIRG 006**
Participants	3,222 women (enrolled between April 2001 and March 2004 from 24 countries including New Zealand) with HER2 positive breast cancer, node positive or high risk node negative (scant description)
Exposure	**AC-TH** 4 cycles AC (60/ 600mg/m^2) followed by 4 cycles of docetaxel 100mg/m^2 and concurrent trastuzumab of unknown dose for one year (n=1074) **TCH:** 6 cycles of doxecetal 75mg/ m^2 and caboplatin AUC6 with concurrent trastuzumab of unknown dose for one year (n=1075)
Comparison	**AC-T** 4 cycles AC (doxorubicin 60mg/ m^2 and cyclophosphamide 600mg/ m^2) followed by 4 cycles of docetaxel 100mg/ m^2 (n=1073)
Outcomes	**Primary outcome**: Disease-free survival **Secondary outcomes:** Overall survival, toxicity, CHF, and pathologic and molecular markers
Time	Median follow-up time 36 months (2nd interim analyses)
Results: RR	AC-T vs AC-TH Disease free survival RR 0.61 (0.54-0.76) AC-T vs TCH Disease free survival RR 0.67 (0.54-0.83) AC-T vs AC-TH Overall survival RR 0.59 (0.42-0.85) AC-T vs TCH Overall survival RR 0.66 (0.47-0.93) *Harms* AC-T vs AC-TH CHF GATE RR 5.0 (1.71-14.57) AC-T vs TCH CHF GATE RR 1.00 (0.25-3.98)
Results: RD	AC-T vs AC-TH 6% (3-9%)absolute benefit DFS (GATE NNT 6) AC-T vs TCH 5% (2-8%) absolute benefit DFS (GATE NNT 21) AC-T vs AC-TH 3% (1-5%) absolute benefit overall survival (GATE NNT 34) AC-T vs TCH 2%(0-4%) absolute benefit overall survival (GATE NNT 44) *Harms* AC-T vs AC-TH 1% (1-2%) absolute increase CHF (GATE NNT 68) AC-T vs TCH no difference CHF GATE
Validity	
Representativeness	Unknown
Allocation	Random assignment into groups -unknown if stratified; allocation concealment not reported
Adjustment	The exposure & comparison groups were similar according to characteristics reported. Adjustments in analyses unknown
Maintained- blind?	Not reported
Compliance	Not reported
Contamination	17 patients of 1073 randomised to control arm (AC-T) crossed over to receive trastuzumab.

Co-intervention	Not reported
Follow-up	Not reported
Blind/Objective outcome	Not reported
ITT analyses	Unable to assess

Comments on study quality

Large randomised control trial showing significant benefit in disease free survival and overall survival with concurrent trastuzumab administered over one year. Study validity unable to be assessed from this powerpoint presentation.

The FinHer Study Joensuu H. et al. 2006

Concurrent pre- anthracycline chemotherapy- trastuzumab for 12 months started in combination with a taxane (total duration 9-10 weeks) prior to anthracycline chemotherapy.

In this study - the hypothesis is that trastuzumab administered before other cardiotoxic therapies and concurrently with potentially synergistic chemotherapy for only nine weeks would limit cardiotoxicity seen in HERA 2005/2007 and Romond et al 2006 (Joint analysis of NSABP B-31 and NCCTG N9831) and maintain efficacy.

Study	**The FinHer Study Joensuu H. et al. 2006**
Participants	Women less than 66yrs old with WHO performance status of 0 or 1, with confirmed HER2 status (positive or negative) who had undergone breast surgery and had at least one positive axillary node or if node negative, a breast tumour at least 20mm diam and negative for progesterone receptors enrolled from 10 participating institutions in Finland Oct 2000-Sept 2003
Exposure	For 232 HER2 +ve women, 3 cycles of docetaxel 100mg/sqm BSA as 1hr infusion day 1 of 21-day cycle OR 3 cycles of vinorelbine 25mg/sqm iv infusion days 1, 8 and 15 of 21-day cycles. Then 3 cycles IV FEC: fluorouracil 600mg/sqm, epirubicin 60mg/sqm and cyclophosphamide 600mg/sq. Nine trastuzumab infusions administered at one-week intervals day 1 of first docetaxel or vinrelbine cycle.(Total n=116)
Comparison	As above but no trastuzumab (n-116)
Outcomes	**Primary outcome**: Disease free survival **Secondary outcomes:** Adverse effects, LVEF, time to distant recurrence and overall survival
Time	3 years (median follow-up)
Results: RR	Disease free survival (both docetaxel and vinorelbine) RR 0.42 (0.21-0.82) Disease free survival (docetaxel) GATE RR 0.27 (0.08-0.9) Disease free survival (vinorelbine) GATE RR 0.56 (0.27-1.18) Overall survival RR 0.41 (0.16-1.08)
Results: RD	13% (3-22%) absolute benefit disease free survival over median 3 year (NNT=7 (4-30)) 7% (95% CI crossed null) absolute benefit in overall survival *Harms* No increase in symptomatic CHF, or serious adverse cardiac events
Validity	
Representativeness	Women with HER2 positive early stage invasive breast cancer who completed surgical therapy and had normal LVEF and no major cardiac disease. The women were Finnish, median age 50 years (ranging from 25-65 yrs) unknown smoking and socioeconomic status and treated in secondary care settings with surgical, radiation, cardiac imaging, pathology and other services available.

Allocation	Stratified randomisation with allocation concealment
Adjustment	The exp and comparison groups are well- balanced except that axillary nodal metastases tended to be more frequent in the trastuzumab group than no-tratsuzumab group.Adjustments were made in the analyses for type of chemotherapy, centre and the number of positive nodes.
Maintained- blind?	Open label- unblinded
Compliance	compliance with full therapy high >95%,
Contamination	Not reported
Co-intervention	Not reported
Follow-up	None lost to follow-up
Blind/Objective outcome measurement	Outcome assessment unblinded. Primary endpoint well described and objective. Secondary outcomes less well described- adverse effects (as recorded on protocol specified forms) and the effect of treatment on LVEF (measured by echocardiography or isotope cardiography). Both are subject to inter-rater variation.
ITT analyses	ITT was conducted with the exception of one woman

Comments on key validity domains

The study was randomised, allocation concealment was reported and outcomes were reasonably objective.However both exposure outcomes and outcome assessment were unblinded. Possible direction of bias for this is lowering of treatment effect due to co-intervention or more aggressive chemotherapy/hormonal therapy for those known to be in the control group (especially if clinicians in the study considered trastuzumab to be an effective drug).
Compliance was very high:- the full dose of trastuzumab was administered in 99.1% of cycles and 93.6% and 96.6%of the protocol specified trastuzumab infusions were delivered to women in the doxecetal and vinorelbine groups respectively.

The outcomes were fairly objective (disease free survival and overall survival) therefore non-blinded outcome assessment may not have a large impact. Indeed, although trastuzumab was known to cause cardiac toxicity , no adverse effects were reported.This may be simply due to the small size of the study (outcome occurring in approx 2-3% of participants in other trials) but the cardiac exclusion criteria were *less rigorous* (see comparison table below) than HERA or NSAP B31 and N9831 and the median age 50yrs (25-65 years) was similar to HERA (median age 49yrs). It may also be due to the timing of trastuzumab treatment and concurrent therapy.

ITT was conducted with the exception of one woman and there were no losses to follow-up which was very important given the small number of outcomes. The effect estimate for disease free survival was similar to the bigger trials (58% RRR) although with wider confidence intervals (less precision) due to small study numbers. Therefore the true effect of this regimen on disease free survival is likely to lie between 18-79% RRR. The study did not have enough power to determine overall survival benefit although the magnitude and direction of effect is similar to disease free survival.

Overall Study Quality

Despite smaller numbers lowering the precision of effect estimates this study had enough power to detect an effect on disease free survival and had a longer follow-up time than other published trastuzumab trials.Reasonable quality overall. Not enough power to determine overall survival- a bigger study is needed.
Other patient outcomes not assessed were longer term effects of cardiac toxicity , differences in quality of life and return to usual daily activities.

Study	**Cardiac exclusion criteria**
Finher Study	Severe hypertension, cardiac disease (including CHF of any degree, arrhythmia requiring regular medications and MI in previous 12 months)
NSAP B31	Angina requiring meds, arrhythmia requiring meds, severe conduction abnormality, clinically significant valvular disease, cardiomegaly on CXR, LVH on echocardiography, poorly controlled hypertension,, Hx of myocardial infarction, CHF or cardiomyopathy
N9831:	Angina requiring medication, arrhythmia requiring medication, severe conduction abnormality, clinically significant valvular disease, cardiomegaly on CXR, poorly controlled hypertension,clinically significant pericardial effusion, Hx of myocardial infarction or cardiomyopathy
HERA	History of documented CHF, coronary artery disease with previous q-wave myocardial infarction, angina pectoris requiring medication, uncontrolled hypertension, clinically significant valvular disease, unstable arrhythmias.