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Trastuzumab: possible publication bias

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Herceptin (trastuzumab) for early breast cancer has caught international attention. Yet its effectiveness may be overestimated, because important clinical trial data from nearly 1000 women have not been published.

Publication bias is of increasing concern, entrenching the use of inferior treatments.[1] This concern now extends to adjuvant trastuzumab (Herceptin) in women with HER2-positive early breast cancer, because a key clinical trial[2] has been only selectively published.[3] As such, patients are being given an important treatment sequence that may be much less effective than currently thought.[4,5]

Adjuvant trastuzumab can be given in two main sequences: ***concurrently with*** or ***sequentially after*** other chemotherapy.[6] Sequential treatment is licensed,[4,5] is standard practice and is the publicly funded regimen in many countries, such as most of Europe (United Kingdom included). One randomised trial (out of six relevant trials[6-8]), by the North Central Cancer Treatment Group (NCCTG), trial NCCTG-N9831,[2] has studied both sequential and concurrent treatments head-to-head, together with a control or usual-care group. However, although this three-group study has important implications for how best to use trastuzumab, it has only been partly published. Data from the 985 women given 12-month sequential trastuzumab in this study are in effect missing,[4,5] despite publication of data from the 12-month concurrent and control groups of the same trial nearly 3 years ago.[9]

Interim results for all three groups of the NCCTG trial were presented orally in 2005 the American Society of Clinical Oncology annual meeting.[2] After 1.5 years' median follow-up, sequential trastuzumab gave a comparatively[4] small 13% relative reduction in disease events compared with usual care—with a reasonable chance of being no better than the control arm (hazard ratio 0.87, 95% CI 0.67–1.13). Conversely, concurrent trastuzumab was significantly more effective than sequential therapy, reducing disease events by a third (0.64, 0.46–0.91)[2].

Soon after, Romond and colleagues published the concurrent and control group results from the NCCTG three-group study with another study of concurrent treatment (the National Surgical Adjuvant Breast and Bowel Project [NSABP] B31 trial) in a retrospectively approved pooled analysis.[9] Limited efficacy data from the individual trials are available in the online appendix to that publication, but do not include the NCCTG sequential-group data. These data are only available as part of a slide presentation on a conference website,[2] and have never been disseminated by peer-reviewed publication[3].

The selective release of data from the NCCTG study has far-reaching implications for women with HER2-positive early breast cancer. Without these data, sequential trastuzumab seems more effective[4] than it probably is. Combining the NCCTG sequential data from the conference slide show[2] with updated results for the other trials of sequential trastuzumab (HERA and PACS-04)[4,7,8] shows a ***treatment effect one-third less*** than initially estimated[10] (HERA 12-month median follow-up, 0.54, 0.43-0.67[11] *vs* HERA 23-month median follow-up[12] with NCCTG-N9831 sequential *vs* control groups[2] with PACS-04[7,8] pooled data, fixed-effects hazard ratio 0.72, 0.67-0.78; 18% absolute difference)—*see Figure One below*. More events will have accrued since 2005, which will further affect pooled estimates.

We understand that although the updated combined analysis for the concurrent group in the NCCTG study and NSABP-B31[13] will soon be published, the NCCTG study's sequential group data will be presented and published only when the number of events is believed sufficient to ensure analysis has the appropriate statistical power.

However, the same criteria for analysing both efficacy and adverse effects should apply to both the sequential and concurrent groups of the NCCTG study. For the NCCTG and NSABP studies, the proper approach would be to publish all efficacy data from both trials separately *(enabling assessment of between-trial variability[31])*, as has been done for cardiotoxicity[14,15]. Instead, what has been published and presented is post-hoc pooled analyses[9,13] limited to concurrent treatment groups that were of appreciably different design.[9,16-18]

The NCCTG three-group study had enough power to detect a statistically significant difference between its concurrent and sequential treatments.[19] But even when trials are underpowered, their data should still be published to inform meta-analysis.[19] Interestingly, the positive results from the NCCTG study's concurrent group were released despite reaching less than half of the prespecified event count required for first interim analysis (140 events occurring vs 331 events required; 663 events were required for final analysis, so 331 is the 50% of events prespecified for the planned first interim analysis).[2] Furthermore, toxicity data from all three NCCTG groups have been considered mature enough to publish, the sequential arm included.[15]

Commentaries in trial reports and reviews consider the NCCTG sequential-group data to be relevant and important.[8-9,12] The 3-year follow-up data have already been presented for the NCCTG concurrent and usual-care groups[13] *(see Figure Two below)*, so are likely to also be available for the sequential group.[13]

Failing to publish inconclusive results can mean wide (and wasteful) use of ineffective treatments, or even unnecessary illness and death if the reported risks of harms are underestimated.[20] Clearly adjuvant trastuzumab is effective,[4,6] but how best to use it appears to have been hampered by some publication choices[3,21] that presently are unclear.

There is a duty of care to trial participants,[3] sponsors, regulators, and the public good to promptly publish outcomes in all exposure groups. This topic is notably underplayed in current statements on good clinical practice for reporting, and also in official directives on the conduct of trials.[32-37]

Is it now time the efficacy data from the entire NCCTG study, with updated events accrued since 2005, see the light of day?

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Conflicts
PHARMAC (SM, JE, SC) is funding a concurrent 9-week regimen of trastuzumab for HER2-positive early breast cancer in New Zealand. CB chairs the Pharmacology and Therapeutics Advisory Committee to PHARMAC. GL has provided legal expert testimony for PHARMAC about trastuzumab. SW has provided external critical appraisals, commissioned by PHARMAC, of the trials of adjuvant trastuzumab.

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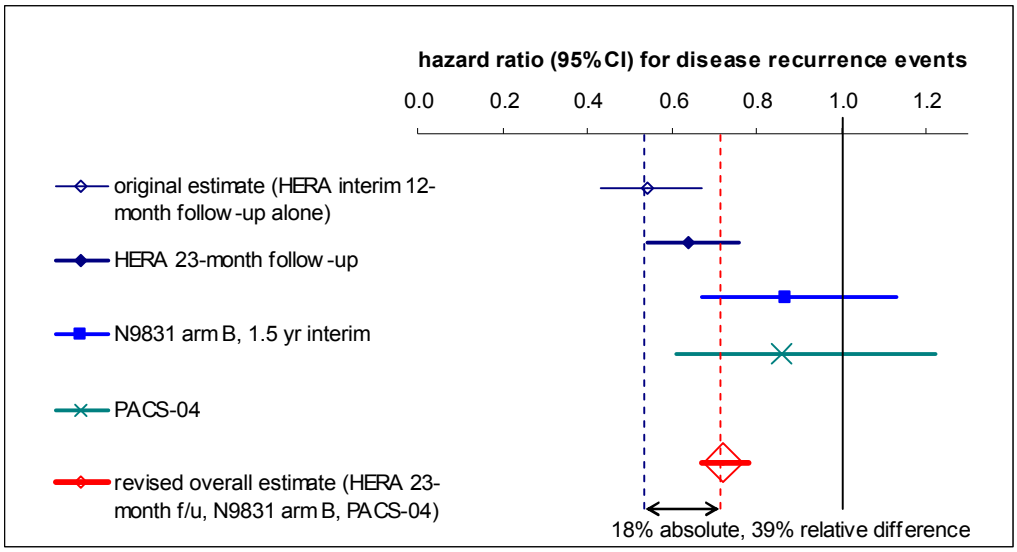
Figures

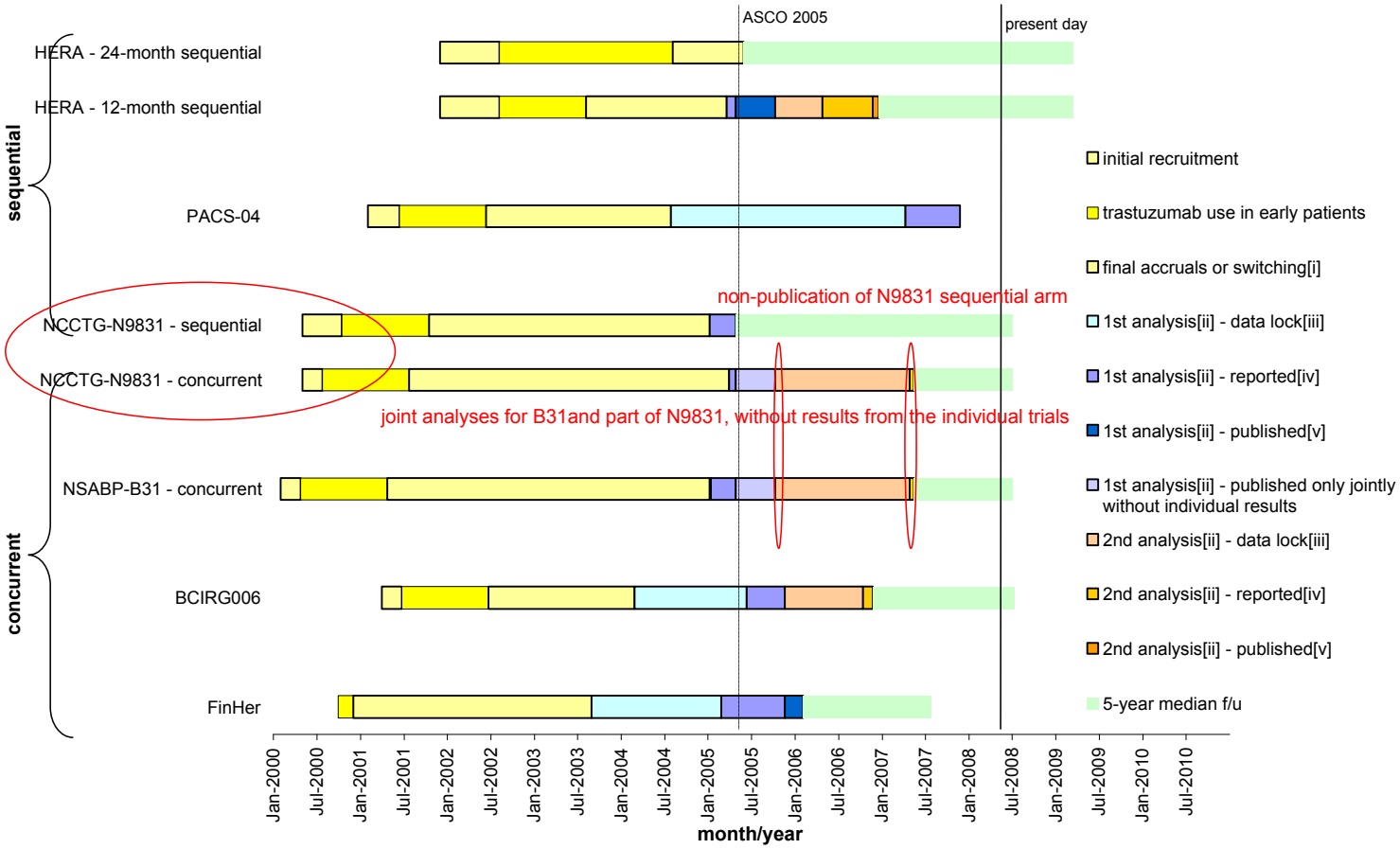
Figure One. Efficacy of sequential 12-month trastuzumab in HER2-positive early breast cancer:



Contributing data:

Trial where adjuvant trastuzumab given sequential to other chemotherapy	tmt n/N vs. cntrl n/N	hazard ratio (95% CI)
(HERA 12-month f/up)	127/1694 vs. 220/1693,	**0.54 (0.43-0.67)**
HERA 23-month f/up	218/1703 vs. 321/1698,	0.64 (0.54-0.76)
NCCTG-N9831 Arm B (sequential)	103/985 vs. 117/979,	0.87 (0.67-1.13)
PACS-04	59/260 vs. 70/268,	0.86 (0.61-1.22)
pooled HERA 23-month f/u / N9831 Arm B (sequential) / PACS-04	380/2948 vs. 508/2945,	**0.72 (0.67-0.78)**

Figure Two. Time course of the RCTs reporting efficacy outcomes for adjuvant trastuzumab in HER2-positive early breast cancer



Five of the six trials reporting disease outcomes with adjuvant trastuzumab compared with standard chemotherapy treatment in HER2-positive early breast cancer (HERA[11,12], NCCTG-N9831[2,9,13], NSABP-B31[2,9,13], FinHer[29], BCIRG006[28]) have reported interim efficacy results, but have varied by the timing of patient accruals, when results were initially reported, and when (if) published. PACS-04[7,8] has reported final results for its HER2 positive patients, having met its preset target event accruals; these remain unpublished.

Results from 5-year median follow-ups (some being final analyses) should be available between mid 2008 and late 2009.

Key:
[i] crossover of patients from standard care arm to trastuzumab arms (HERA), or crossover from standard care or sequential trastuzumab arms to concurrent trastuzumab arm (N9831)
[ii] interim efficacy analysis
[iii] data lock – date that database closed and the data were locked for analysis
[iv] reported – date that results first presented at conference or reported in lay media
[v] published – date that results from the individual trial first published in peer reviewed journal

A seventh study, ECOG E2198, which compared 12 months with 10 weeks trastuzumab given concurrently with paclitaxel, was presented as a poster at the San Antonio Breast Cancer Symposium in 2006 (Sledge et al, http://www.abstracts2view.com/sabcs06/view.php?nu=SABCS06L_561). However, this was a pilot study not designed to test efficacy nor powered to determine equivalence and has not reported outcomes against standard chemotherapy treatment.

Notes

1. *Publication bias emerges when the published trials do not represent all the trials undertaken for a particular intervention, usually because statistically significant results tend to be submitted and published more frequently than indeterminate results.[22,23] Recent examples include trials relating to celecoxib[24,25] and paroxetine.[1,26,27]*

2. *Trastuzumab (Herceptin) was discovered and developed by Genentech, a U.S. biotechnology company in which Roche holds a 67 percent stake. In July 1998, Genentech granted Roche exclusive marketing rights for Herceptin outside the United States.*

3. *A number of countries have licensed a sequential 12-month trastuzumab treatment regimen. There appears to be a division between the USA and the rest of the world for sequencing (sequential vs. concurrent), according to which company markets trastuzumab.*

   In most countries, assessment of funding a medicine is limited to the licensed indication which is largely dictated by data provided by, and supported by, the supplier. In turn, many countries have public funding only for licensed regimens.

   In the US, trastuzumab was marketed by Genentech, who gained licensing from the FDA for concurrent 12 month treatment (http://www.gene.com/gene/products/information/oncology/herceptin/insert.jsp). Only recently Genentech sought and gained licensing approval for sequential in the US.[5] Hence, use of trastuzumab there will have been predicated by the licensed sequence (concurrent).

   Roche has marketed trastuzumab in most of the rest of the world, including Europe and Canada, gaining licensing for the sequential regimen after completion of surgery and chemotherapy. The EMEA SmPC licensing states that trastuzumab is indicated for the treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) – i.e. sequential treatment.(http://www.emea.europa.eu/humandocs/PDFs/EPAR/Herceptin/H-278-PI-en.pdf)

   We understand most EU countries only fund the sequential regimen, being that regimen licensed by the EMEA. This includes the United Kingdom.

   In England/Wales, the NICE guidance refers to the EMEA licensing (being for 12 months sequential), and based its appraisals (and hence recommendation that PCTs fund) on 12 month sequential treatment – the EMEA registered regimen, requested by Roche supported by the HERA trial data alone. The NICE guidance states "Trastuzumab treatment should be offered as an option for women with early-stage HER2-positive breast cancer after they have had surgery and chemotherapy (and sometimes radiotherapy)." (http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11586).

   In Australia there are a number of licensed and funded options for using trastuzumab, including long and short duration, and using it concurrently with, or sequentially to, taxane chemotherapy. (http://www.pbs.gov.au/pi/ropherce10406.pdf, http://www.pbs.gov.au/html/healthpro/search/results?term=herceptin&scope=PBS+STATIC&form-type=simple).

4. *Six RCTs have reported disease outcomes for adjuvant trastuzumab compared with standard chemotherapy treatment alone in HER2-positive early breast cancer[6-8] – HERA[11,12], PACS-04[7,8], NCCTG-N9831[2,9,13], NSABP-B31[2,9,13], BCIRG 006[28], and FinHer[29]. All six trials are open-label. Five have reported interim efficacy results (all except PACS04), but they have varied by the timing of patient accruals, when results were initially reported, and when (if) published. PACS-04 has reported final results for its HER2 positive patients, having met its preset target event accruals; these remain unpublished.Results from 5-year median follow-ups (some being final analyses) should be available between mid 2008 and late 2009 (see Figure Two above).*

5. *Interim results have known risks of overstating true treatment effects[16, 30] , as has also occurred elsewhere with adjuvant trastuzumab (e.g. in the HERA trial).[4]*

6. *NCCTG-N9831's usual care chemotherapy arm (Arm A) treated patients with doxorubicin/ cyclophosphamide, followed by paclitaxel, AC-T (n=1162 patients). The trastuzumab sequential to (after) chemotherapy arm (Arm B) used AC-T followed by 12 months trastuzumab given sequentially to paclitaxel (n=985). The trastuzumab given concurrently with chemotherapy arm (Arm C) used doxorubicin/ cyclophosphamide (AC) followed by 12 months trastuzumab started concurrently with paclitaxel (n=979).[2]*

7. *'Disease events' in this Comment derive from disease-free survival (DFS) in all six RCTs that have reported outcomes for adjuvant trastuzumab in HER2-positive early breast cancer studies. DFS incorporates both recurrence of breast cancer and death without recurrence.*

8. *The NCCTG-N9831 study has informally reported the outcomes for 985 women treated with trastuzumab sequentially. The failure to show significant improvements in DFS with sequential treatment (Arm B) compared with standard care (Arm A) may not be simply due to the play of chance, with fewer events and patients for analysis[6]. It may actually show a lower efficacy of the sequential approach (with the hazard ratio being only 0.87 on interim analysis[2]).*

9. *The N9831 and B31 trials of concurrent regimens in the Romond 2005 interim analysis[9] differed in patient eligibility (high risk negative node status); methods of randomisation allocation; taxane regimens, anthracycline regimens, sequencing with radiotherapy, sequencing with hormonal therapy, aromatase inhibitor types, and when they started to be used in the trials; recommendations for post surgical radiotherapy; and primary endpoints (disease free survival (DFS) for N9831, overall survival for B31).[9,16-18]*

10. *The posting of these important results for the sequential arm of NCCTG-N9831 only on specialist conference websites makes them unlocatable on Medline searches etc. and they are not subject to peer review and other scrutiny.*

11. *The non-publication of Arm B has extended to information about cross-over of patients from the control arm and*

sequential arms (A, B) not being available on public record – which may be important for the interpretation of ongoing publications of Arm C results. The N9831 data monitoring committee was sufficiently impressed by the interim results of the N9831 trial to offer subjects not only in Arm A (control) but also B (sequential) the opportunity to have concurrent trastuzumab (i.e. crossover to Arm C) – in its view an ethical decision based on the results it viewed. Arm A patients could switch to trastuzumab (arms B or C) from April 2004, and Arm B patients could switch to concurrent trastuzumab (Arm C) from January 2005 [letter from RocheNZ to PHARMAC dated 6 March 2007].

12. *Concerns around whether NCCTG-N9831 was sufficiently powered prospectively to assess sequential treatment can be allayed by the trial's results as reported, albeit unpublished. The statistically significant result presented at ASCO 2005 for the concurrent versus sequential arms (HR 0.64, 95% CI 0.46- 0.91)[2] means that it emerged that the study was indeed sufficiently powered to detect this difference. This is where once results become available then the power of the trial is expressed in its treatment effect's confidence interval, rendering prospective power considerations to be obsolete.[19] The 0.46-0.91 confidence interval for the DFS hazard ratio comparing N9831's concurrent arm with its sequential arm (stratified logrank 2p value 0.0114) was derived from just 23% (n=137) of the 590 pooled events in these two arms that the prospective power calculations had predetermined to be necessary[2].*

13. *As noted in the NCCTG-N9831 ASCO conference presentation[2], during patient accrual, at any time patients in Arm C (concurrent) would have received three additional months of trastuzumab compared with patients in Arm B (sequential). This difference in the phasing of exposure to trastuzumab treatment has the potential to understate both the efficacy and adverse effects of sequential treatment compared with concurrent treatment. Presumably this issue will have been recognised and accounted for in pre-planned trial protocol for statistical analysis, and would be at least be discussed in a formal peer-reviewed publication of the results.*

14. *The NCCTG-N9831 Arm B vs. A events were analysed at around April 2005, compared with May 2006[12] for the 23-month median follow-up for HERA trial. Had the N9831 Arm B vs. Arm A results been re-analysed and then presented at the same time as were HERA 23-month median follow-up data at the 2006 ASCO conference, the additional numbers of events could appreciably influence the weight given to N9831 Arm B in estimates of overall efficacy of sequential trastuzumab.*

    However, this needs to be balanced against attrition bias, where the inclusion of patients pre-surgery and radiotherapy in N9831 means that numbers of treatment failures (in all arms) are proportionately greater than in HERA (patients in HERA were enrolled following the completion of surgery and radiotherapy).

15. *Publishing all data from each of the arms of the NCCTG-N9831 and NSABP-B31 trials separately would also enable assessment of between-trial variability. Identifying variation in response between patient groups/study designs is important for systematic reviews.*

    Often patients recruited into separate trials are included in a combined or pooled analysis, extending for example what happens when results from separate centres are combined in a multi-centre trial[31] (albeit multi-centre trials are designed prospectively). However, it is also necessary and common practice to assess whether there are systematic differences between trials or centres.

    When trials are only published in individual patient data meta-analyses or as combined analysis, and are then added to a further meta-analysis, the effect is to greatly reduce the variance and potentially the heterogeneity. In effect, this produces a meta-analysis of meta-analyses. This means, for instance, that two small studies can be given undue weight and make the overall weighted average appear much more internally consistent than it actually is.

    Simply pooling the data therefore reduces the influence of between-trial variability in the final estimate of effect. Compared with the results of standard meta-analytic methods, pooling the data may considerably understate the level of uncertainty.[31]

References

1. Geddes J, Szatmari P, Streiner D. The worm turns: publication bias and trial registers revisited. Evid Based Ment Health 2004;7: 98-99. http://ebmh.bmj.com/cgi/content/full/7/4/98
2. Perez EA, Suman VJ, Davidson N, et al on behalf of NCCTG, ECOG, SWOG, CALGB. Further analysis of NCCTG-N9831, May 2005 update. Slide presentation presented at the 45th annual meeting of the American Society of Clinical Oncology, Orlando, FL, USA, May 13–17, 2005. http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Virtual+Meeting?&vmview=vm_session_presentations_view&confID=34&sessionID=934 (accessed May 8, 2007).
3. Krzyzanowska MK, Pintilie M, Tannock IF. Factors associated with failure to publish large randomized trials presented at an oncology meeting. JAMA 2003; 290: 495-501. http://jama.ama-assn.org/cgi/content/full/290/4/495
4. Hind D, Pilgrim H, Ward S. Questions about adjuvant trastuzumab still remain. Lancet 2007; 369: 3-5. http://www.thelancet.com/journals/lancet/article/PIIS0140673607600004X/fulltext
5. Food and Drug Administration. HERCEPTIN (trastuzumab) label approved on 01/18/08, FDA Application No. (BLA) 103792. http://www.fda.gov/cder/foi/label/2008/103792s5175lbl.pdf (accessed May 8, 2007).
6. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. N Engl J Med 2007; 357: 39-51. http://content.nejm.org/cgi/content/full/357/1/39
7. Spielmann M, Roché H, Humblet Y, et al. 3-year follow-up of trastuzumab following adjuvant chemotherapy in node positive HER2-positive breast cancer patients: results of the PACS-04 trial. San Antonio Breast Cancer Symposium, San Antonio, TX, USA, December 13-16, 2007. http://www.abstracts2view.com/sabcs/view.php?nu=SABCS07L_661 (accessed May 11, 2008).
8. Spielmann M, Roché H, Humblet Y, et. al. Trastuzumab following adjuvant chemotherapy in node positive, HER2-positive breast cancer patients: 4-year follow-up results of the PACS-04 trial. San Antonio Breast Cancer Symposium, San Antonio, TX, USA, December 13-16, 2007. http://www.sabcs.org/ Daily Slide Reviewer: Presentations: Day 4: General Session 7 (accessed May 11, 2008).
9. Romond, EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER-2 positive breast cancer. N Engl J Med 2005; 353: 1659-72. http://content.nejm.org/cgi/content/full/353/16/1673; on-line supplementary appendix at http://content.nejm.org/cgi/data/353/16/1673/DC1/1
10. Metcalfe S, Evans J, Priest G. PHARMAC funding of 9-week concurrent trastuzumab (Herceptin) for HER2-positive early breast cancer. N Z Med J 2007; 120: U2593. http://www.nzma.org.nz/journal/120-1256/2593/; Appendix 4: Clinical effectiveness http://www.nzma.org.nz/journal/120-1256/2593/Afour.pdf
11. Piccart-Gebhart M.J. Procter M, Leyland-Jones B, et al, for the Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659-72. http://content.nejm.org/cgi/content/full/353/16/1659
12. Smith I, Procter M, Gelber RD, et al, for the HERA study team. 2 year follow up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007; 369: 29-36. http://www.thelancet.com/journals/lancet/article/PIIS0140673607600282/fulltext
13. Perez EA, Romond EH, Suman VJ, et al, NCCTG/NSABP. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer. 2007 ASCO Annual Meeting Proceedings Part I. J Clin Oncol 2007; 25 (suppl 18): 512 (abstr). http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=47&abstractID=35229
14. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005; 23: 7811-19. http://jco.ascopubs.org/cgi/content/full/23/31/7811
15. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008; 26: 1231-38. http://jco.ascopubs.org/cgi/content/full/26/8/1231
16. Lancet. Herceptin and early breast cancer: a moment for caution. Lancet 2005; 366: 1673. http://www.thelancet.com/journals/lancet/article/PIIS0140673605676702/fulltext
17. Sledge GW. Targeting HER-2 in the adjuvant setting. 45th annual meeting of the American Society of Clinical Oncology, Orlando, FL, USA, May 13–17, 2005. http://media.asco.org/player/default.aspx?LectureID=5813&conferenceFolder=VM2005&SessionFolder=SS11&slideonly=yes&TrackID=N929&LectureTitle=Discussant%3a%20NCI%2fHERA%20Trials&Key=vm_34_1_934_5813&SpeakerName=Chair%3a%20George%20W.%20Sledge%2c%20Jr.%2c%20MD&mediaURL=%2fmedia&ServerName=media.asco.org&max=25&ext=jpg&useASX=false&playtype=&playtype=&playtype= (accessed May 8, 2008).
18. Perez EA. New data related to monoclonal antibody therapy for breast cancer–ASCO 2005. 45th annual meeting of the American Society of Clinical Oncology, Orlando, FL, USA, May 13-17, 2005. http://professional.cancerconsultants.com/conference_asco_2005.aspx?id=34419 (accessed May 8, 2008).
19. Schulz KF, Grimes DA. Sample size calculations in randomised trials: mandatory and mystical. Lancet 2005;

365: 1348-53.
http://www.thelancet.com/journals/lancet/article/PIIS0140673605610343/fulltext

20. *Chalmers I. Underreporting research is scientific misconduct. JAMA 1990;263:1405-1408.*

21. *Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998;279:281-286. http://jama.ama-assn.org/cgi/content/full/279/4/281*

22. *Schulz KF, Grimes DA. Sample size calculations in randomised trials: mandatory and mystical. Lancet. 2005;365:1348-53. http://www.thelancet.com/journals/lancet/article/PIIS0140673605610343/fulltext*

23. *Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. Health Technol Assess. 2000;4:1-115. http://www.hta.ac.uk/fullmono/mon410.pdf*

24. *Juni P, Rutjes AWS, Dieppe PA. Are selective COX-2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? BMJ 2002; 324:1287-1288. http://bmj.com/cgi/content/full/324/7349/1287*

25. *Caldwell B, Aldington S, Weatherall M, Shirtcliffe P, Beasley R. Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis. J R Soc Med. 2006;99:132-40. http://www.jrsm.org/cgi/content/full/99/3/132*

26. *Whittington CJ, Kendall T, Fonagy P, et al. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004;363:1341-5. http://www.thelancet.com/journals/lancet/article/PIIS0140673604160431/fulltext*

27. *Depressing research. Lancet 2004;363:1335. http://www.thelancet.com/journals/lancet/article/PIIS0140673604160807/fulltext*

28. *Slamon D, Eiermann W, Robert N, et al, on behalf of the BCIRG 006 Investigators. Phase III Trial Comparing AC-T with AC-TH and with TCH in the Adjuvant Treatment of HER2 positive Early Breast Cancer Patients: Second Interim Efficacy Analysis. Slide presentation ASCO annual meeting 2006, available online at http://www.bcirg.org/NR/rdonlyres/eqkdodq2dy7t557o7s6uvj7ytpe6qcfg5qmh2ely6hnhh5pjlabz3nd6jddlnao7qoikej3edohsijyiisfvp367uuc/BCIRG%20006+2nd+Interim+Analysis.pdf*

29. *Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, et al; FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354:809-20. http://content.nejm.org/cgi/content/full/354/8/809*

30. *Montori VM, Devereaux PJ, Adhikari NKJ, et al. Randomized trials stopped early for benefit: a systematic review. JAMA 2005;294:2203-2209. http://jama.ama-assn.org/cgi/content/full/294/17/2203*

31. *Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L. Hormonal therapies for early breast cancer: systematic review and economic evaluation. Health Technol Assess 2007;11(26). www.hta.ac.uk/fullmono/mon1126.pdf Appendix 4 Statement from NICE DSU (p 115)*

32. *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline. Guideline for good clinical practice E6 (R1), 1996.*

33. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official J Eur Communities, L121:34–44, 2001.*

34. *Directive 2005/28/EC of the European Parliament and of the Council of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Official J Eur Communities, L91:13–19, 2005.*

35. *Statutory Instrument 2004 No. 1031: The Medicines for Human Use (Clinical Trials) Regulations 2004. HM Government. Stationery Office, London, 2004. ISBN 0110490487.*

36. *Statutory Instrument 2006 No. 1928: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006. HM Government. Stationery Office, London, 2006.*

37. *Description of the Medicines for Human Use (Clincal Trials) Regulations 2004. Medicines and Healthcare Products Regulatory Agency, 2004.*