Herceptin – a summary of the evidence at August 2008

Herceptin (trastuzumab) is a relatively new monoclonal antibody treatment developed to treat HER2 positive breast cancer. It can be used both for advanced (metastatic) and early stage HER2 positive breast cancer.

Herceptin works via the HER2 receptor that lies on the surface of cells. This receptor is responsible for controlling growth and repair in cells and is, in a variety of forms, widespread in the human body. In HER2 positive breast cancer cells this receptor is over expressed. Herceptin (trastuzumab) is a 'Monoclonal AntiBody' (hence 'mab') that blocks the effects of the HER2 receptor in cancers and elsewhere, including the heart.

Because it is relatively new, it is not yet clear which way of using Herceptin produces the best results in HER2-positive early breast cancer. Different clinical trials have looked at different ways of using the drug. There are two central questions about how best to use Herceptin:

- Sequencing (before, concurrent with, or after other chemotherapy); and
- Duration (9 weeks, 6, 9, 12 or 24 months treatment).

It is clear that Herceptin provides some additional benefit and risks for some patients over standard chemotherapy alone. Data is continuing to emerge about the magnitude of these benefits and risks and how long they last.

No head-to-head trials have shown whether long or short duration therapy is more effective. However, there are ways to compare the current evidence from the available different trials and these comparisons have been conducted by PHARMAC and some other pharmaceutical assessment agencies in other countries.

The majority of studies show that Herceptin improves disease-free survival (DFS) compared with standard chemotherapy. In general longer term follow-up data on these studies suggest this benefit may lessen over time.

The main body of evidence for Herceptin in HER2 positive early breast cancer comprises four studies examining concurrent treatment (NCCTG N9831, NSABP B-31, BCIRG006 and FinHer) and three studies examining sequential treatment (HERA, NCCTG N9831 and PACS04). Here is a summary of the key results of these main trials:

- HERA trial (sequential 12 months treatment) – when measured after 2 years, compared with standard chemotherapy, for every 100 women treated with Herceptin, six more would avoid having their tumours recur or death (disease events), and nearly two extra deaths from any cause would be avoided.

- NCCTG N9831 Arm B (sequential 12 month treatment) – no benefit (a 1.5% improvement in disease-free survival, which was not significantly better than standard chemotherapy) after 18 months.

- PACS04 (sequential 12 month treatment) – no benefit (a 3.4% improvement in disease-free survival, which was not significantly better than standard chemotherapy; a -0.4% benefit for overall survival, statistically worse than standard chemotherapy) after 4 years.

- Romond/Perez studies, combined data from NSABP B-31 and NCCTG N9831 Arm C (concurrent 12 months treatment) – for every 100 women treated with Herceptin compared with standard chemotherapy, nearly 9 would avoid having their tumours recur

or death (disease events), and nearly 3 additional deaths from any cause would be avoided (measured at 3 years follow up).

- BCIRG006 (concurrent 12 months treatment) – for every 100 women treated with Herceptin compared with standard chemotherapy, 6 would avoid having their tumours recur or death (disease events), and nearly 3 additional deaths from any cause would be avoided (measured at 3 years follow up).
- FinHer (concurrent 9 weeks treatment) – for every 100 women treated with Herceptin, compared with standard chemotherapy, nearly 13 more women would avoid having their tumours recur or death (disease events), when measured after three years.

The larger 12 month studies provide greater certainty of the *numerical* accuracy of the evidence, providing greater confidence in the result. Smaller studies, such as FinHer, have wider confidence intervals than larger studies; however the results are still statistically significant and valid and show a good benefit for the concurrent 9 week treatment compared with chemotherapy alone.

The Pharmacology and Therapeutics Advisory Committee (PTAC) consider that, overall, the evidence reported to date demonstrates:

- no statistically significant benefit of 12 months sequential Herceptin treatment in N9831 over 18 months median follow-up and PACS04 over four years median follow-up; and
- an apparent waning of benefit with 12 months sequential Herceptin in the HERA study over two years and 12 months concurrent Herceptin in BCIRG006 over three years; and
- maintained benefit for the 12 months concurrent Herceptin in B31/N9831 combined over three years; and
- FinHer has yet to report further follow-up data beyond the 3-year median follow-up results.

The Cancer Treatments Subcommittee of PTAC (CaTSoP) consider that evidence from all concurrent studies was consistent with Herceptin producing a relative risk reduction in disease recurrence of around 50% and around 33% in overall survival. CaTSoP further considered that results of the FinHer study supported a similar overall survival benefit; however, members noted that this benefit did not reach statistical significance, likely due to the small size of the FinHer study.

The following summary tables and figures show all the available data on disease free survival and overall survival from relevant trastuzumab clinical trials (HERA, NCCTG N9831, NSABP B-31, FinHER, BCIRG006 and PACS04) plotted against median follow-up time.

Figures 1 and 2 show how effective Herceptin treatment has been in the trials over time. These are for disease free survival and overall survival (OS) respectively. On the graphs the higher the line the less effective Herceptin is, where the horizontal (1.0) line means Herceptin is same as standard treatment. Vertical lines on the graphs indicate the confidence intervals around the data points. The narrower the confidence interval, the more sure are the results. If the line is below the horizontal (1.0) line and the vertical confidence interval line does not cross the horizontal (1.0) line Herceptin treatment is better than standard chemotherapy; however if the line or vertical confidence interval line crosses the horizontal (1.0) line Herceptin treatment is no better than standard chemotherapy (and in some cases is worse than no treatment).

Figure 1 shows, for instance in the HERA sequential 12 month trial, there is some waning of effect for disease free survival, being less effective when patients were followed up for a median of two years than when they were measured at one year; while FinHer's concurrent 9 week results span a median of three years' follow-up.

Figure 3 and Table 1a shows the extent of the extra improvements in disease free survival through using trastuzumab for the most recently reported results. Table 1b shows improvements in overall survival. The graph (Figure 3) shows both the best estimates and the range within which we can be sure the true value lies (each result's 95% confidence interval). For instance, with the PACS04 trial of sequential 12 month Herceptin, overall the best estimate is a 3% reduction in disease events over 4 years (23% for trastuzumab patients vs. 26% for standard care), with the 95% confidence range being as high as 9% and as low as -5% (i.e. 5% worse than standard care).

Table 1a: Disease events, DFS absolute improvements (disease event absolute risk reductions) and DFS hazard reductions (HRs) (with 95% CIs) for adjuvant trastuzumab trials

	median f/u (years)	events/pts tmt	cntrl	ARR	hazard ratio HR	-95% CL	+95% CL
sequential post-anthracyclines							
HERA	1.9	218/1703	321/1698	6.1%	**0.64**	0.54	0.76
N9831 sequential arm	1.5	103/985	117/979	1.5%	**0.87**	0.67	1.13
PACS-04	4.0	59/260	70/268	3.4%	**0.86**	0.61	1.22
overall	*2.0*	*380/2948*	*508/2945*	*4.4%*	***0.72***	*0.67*	*0.78*
concurrent post-anthracyclines							
B31 (2.4 yr interim 1)	2.4	83/864	171/872	10.0%	**0.45**	0.35	0.58
N9831 arm C (1.5 yr interim 1)	1.5	50/808	90/807	5.0%	**0.54**	0.38	0.76
BCIRG 006 arm AC-TH	3.0	128/1074	192/1073	6.0%	**0.61**	0.48	0.76
overall	*2.4*	*261/2746*	*453/2752*	*7.0%*	***0.53***	*0.46*	*0.62*
concurrent pre-anthracyclines							
FinHer	3.0	12/115	27/116	12.8%	**0.42**	0.21	0.83

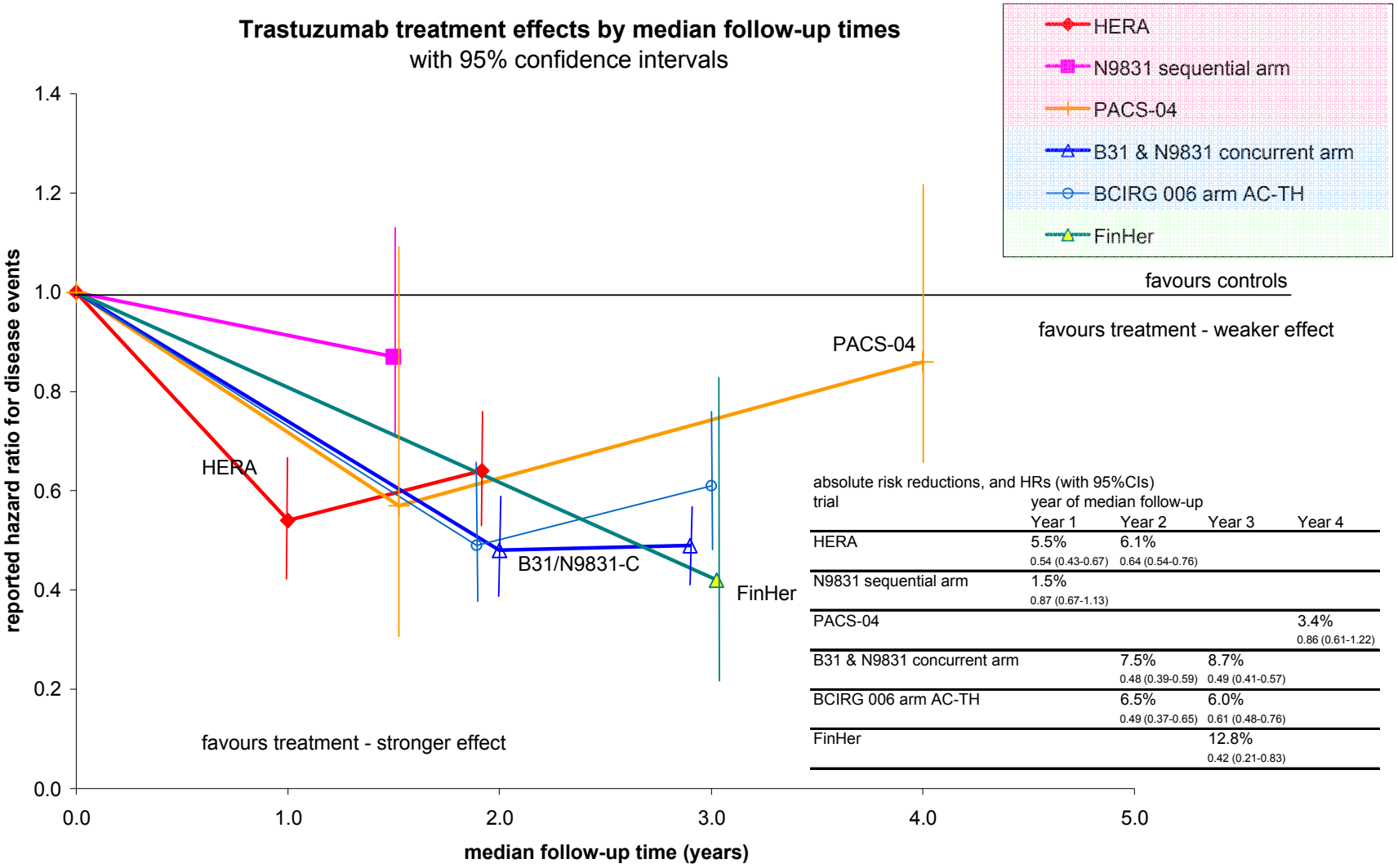
ARR = absolute risk reduction (the difference between the control (standard care) and treatment event rates (%))
HR = hazard ratio

Table 1b: All-cause deaths, overall survival (OS) absolute improvements (absolute risk reductions in deaths) and OS HRs (with 95% CIs) for adjuvant trastuzumab trials

	median f/u (years)	events/pts tmt	cntrl	ARR	hazard ratio HR	-95% CL	+95% CL
sequential post-anthracyclines							
HERA	1.9	59/1703	90/1698	1.8%	**0.66**	0.47	0.91
N9831 sequential arm	1.5	36/985	43/979	0.7%	**0.85**	0.55	1.33
PACS-04	4.0	2/260	1/268	-0.4%	**2.06**	0.61	6.99
overall	*2.0*	*97/2948*	*134/2945*	*1.3%*	***0.76***	*0.65*	*0.88*
concurrent post-anthracyclines							
B31 & N9831 arm C (2.9 yr median f/u)	2.9	102/1979	156/1989	2.7%	**0.65**	0.51	0.84
BCIRG 006 arm AC-TH	3.0	49/1074	80/1073	2.9%	**0.59**	0.42	0.85
overall	*2.9*	*151/3053*	*236/3062*	*2.8%*	***0.63***	*0.51*	*0.77*
concurrent pre-anthracyclines							
FinHer	3.0	6/115	14/116	6.9%	**0.41**	0.16	1.08

ARR = absolute risk reduction. HR = hazard ratio

Figure 1



absolute risk reductions, and HRs (with 95%CIs)

trial	year of median follow-up			
	Year 1	Year 2	Year 3	Year 4
HERA	5.5% 0.54 (0.43-0.67)	6.1% 0.64 (0.54-0.76)		
N9831 sequential arm	1.5% 0.87 (0.67-1.13)			
PACS-04				3.4% 0.86 (0.61-1.22)
B31 & N9831 concurrent arm		7.5% 0.48 (0.39-0.59)	8.7% 0.49 (0.41-0.57)	
BCIRG 006 arm AC-TH		6.5% 0.49 (0.37-0.65)	6.0% 0.61 (0.48-0.76)	
FinHer			12.8% 0.42 (0.21-0.83)	

Figure 2

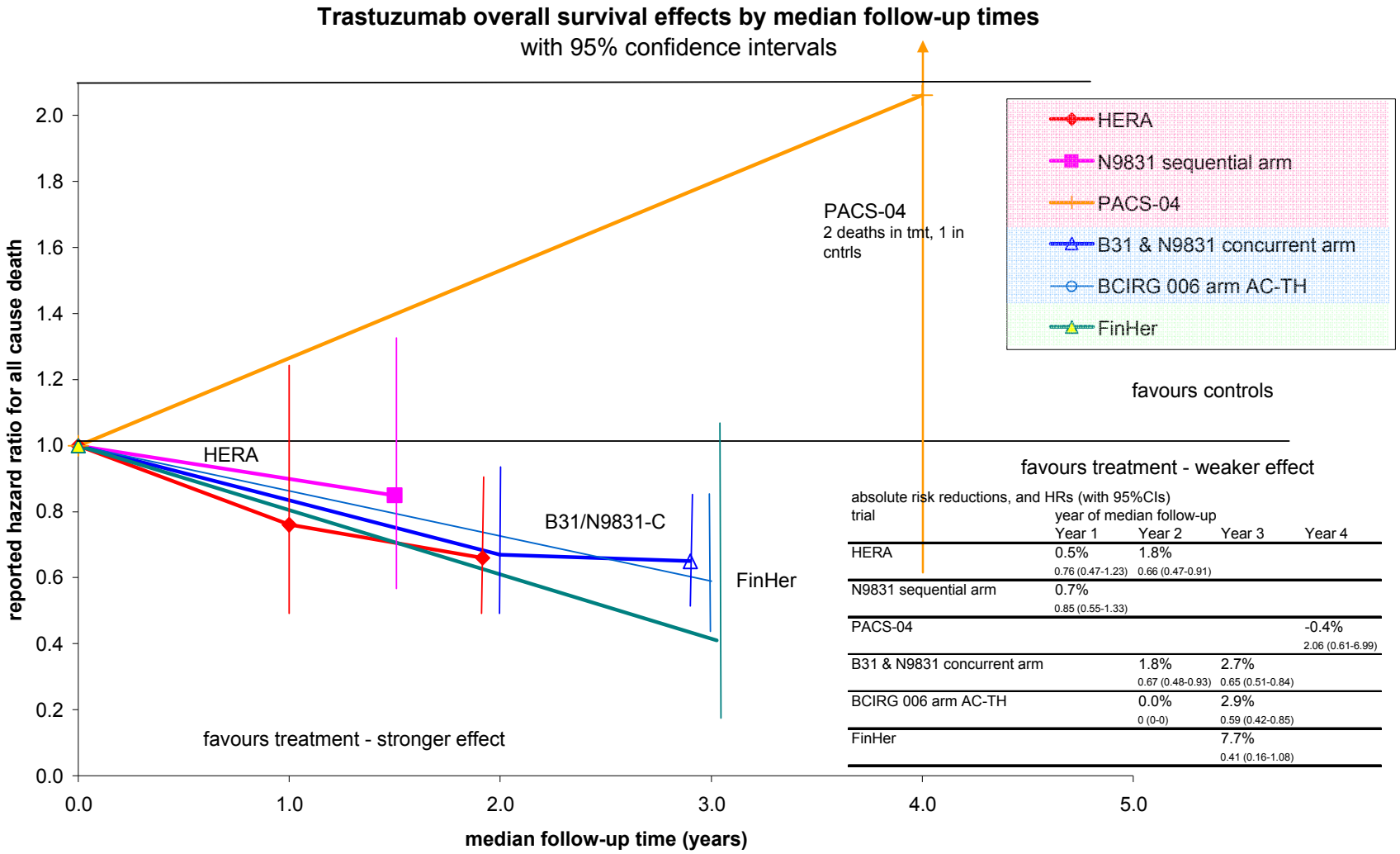
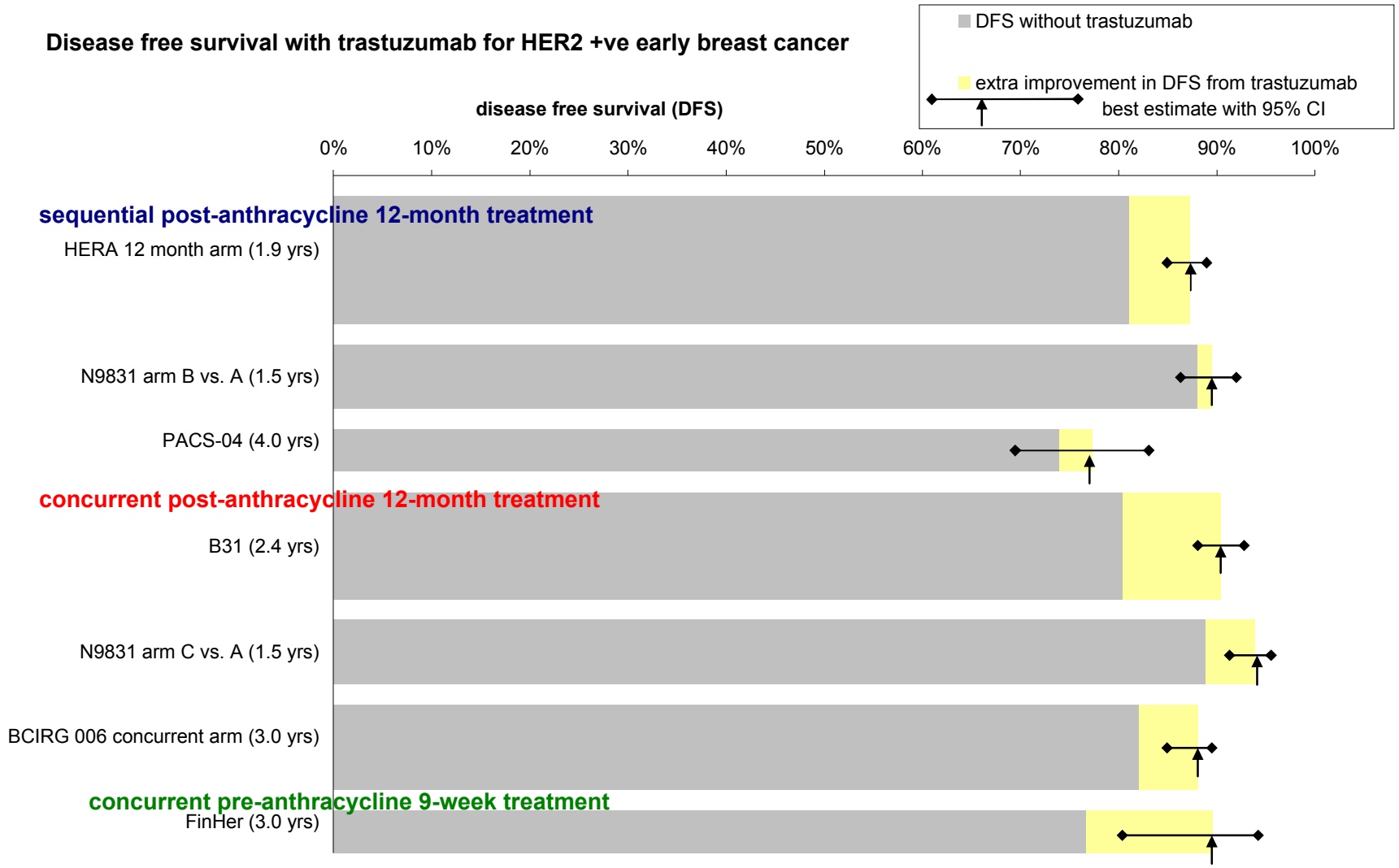

Trastuzumab overall survival effects by median follow-up times
with 95% confidence intervals
reported hazard ratio for all cause death
median follow-up time (years)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
0.0
1.0
2.0
3.0
4.0
5.0
HERA
N9831 sequential arm
PACS-04
B31 & N9831 concurrent arm
BCIRG 006 arm AC-TH
FinHer
PACS-04
2 deaths in tmt, 1 in cntrls
HERA
B31/N9831-C
FinHer
favours controls
favours treatment - weaker effect
favours treatment - stronger effect
absolute risk reductions, and HRs (with 95%CIs)
trial
year of median follow-up
Year 1
Year 2
Year 3
Year 4
HERA
0.5%
0.76 (0.47-1.23)
1.8%
0.66 (0.47-0.91)
N9831 sequential arm
0.7%
0.85 (0.55-1.33)
PACS-04
-0.4%
2.06 (0.61-6.99)
B31 & N9831 concurrent arm
1.8%
0.67 (0.48-0.93)
2.7%
0.65 (0.51-0.84)
BCIRG 006 arm AC-TH
0.0%
0 (0-0)
2.9%
0.59 (0.42-0.85)
FinHer
7.7%
0.41 (0.16-1.08)

Figure 3



individual results for concurrent 12 month treatment trials B31 and N9831 as reported separately in the first combined interim analysis (Romond NEJM 2005)

Publication bias

PTAC considered that data for Herceptin in HER2 positive early breast cancer has been, and continues to be, subject to unacceptable publication bias. Given this unacceptable publication bias PTAC felt compelled to consider all relevant data sources regardless of format or detail.

PTAC noted the non-publication to date of results that have been presented at major conferences (N9831 sequential arm, BCIRG006 all analyses, B31/N9831 concurrent 2.9 year follow-up and PACS04), the comparatively poor dissemination of negative results, and the non-reporting of potentially important data (e.g. from the HERA 24 month Herceptin arm).

PHARMAC note that neither MedSafe nor the majority of international and national treatment guidelines take into account these important unpublished data, therefore, some oncologists may not be even aware of the negative results for Herceptin, including those of the unpublished N9831 sequential arm and the PACS04 trial and the waning of benefit demonstrated in BCIRG006 (seen also in the published data for HERA).

The effect of publication bias is outlined in the recent Lancet article (Metcalfe et al. Lancet 2008;371:1646-8.) which expressed concerns about Herceptin publication bias.

> *'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. Clearly adjuvant trastuzumab is effective but how best to use it appears to have been hampered by some publication choices that presently are unclear. There is a duty of care to trial participants, sponsors, regulators, and the public good to promptly publish outcomes in all exposure groups.'*

Other aspects the quality of evidence

PTAC considered that there was still uncertainty about the best way of administering Herceptin in terms of optimal treatment sequencing, duration, minimising cardiovascular toxicity, and long-term clinical outcomes. It also stated that no new information had been presented that has demonstrated any additional health benefit for 12 months treatment (sequential or concurrent) over the currently funded concurrent 9 week regimen.

Emerging evidence is that sequential 12 months is the least effective way to use Herceptin. For concurrent 12 months trastuzumab, PTAC noted that although the weight of evidence supports its use, there are on balance overriding concerns about its durability of efficacy, increased cardiotoxicity, its high cost, and the lack of conclusive evidence of additional health gain over the 9-week regimen.

The term "weight of evidence" for concurrent 12 months trastuzumab refers to its greater statistical certainty (precision with narrower confidence limits) compared with that of concurrent 9 weeks treatment. This results in statistically significant improvements in overall survival not occurring with 9 week treatment.

Debates around the "certainty" of the evidence around Herceptin have related largely to the numbers of patients enrolled in the various clinical trials. There are, however, many

factors that are important to assessing the quality and robustness of the clinical data supporting the various treatment options, of which numerical precision is only one. Bias for other reasons (beyond the play of chance) can just as easily give false results. It is therefore incorrect to differentiate study evidence solely on trial size at the expense of other aspects of trial validity.

A common misconception is that a statistically significant result is always of practical significance, or demonstrates a large effect in the population. Given a sufficiently large sample size (i.e. the number of patients treated), extremely small and non-notable differences can be found to be statistically significant, and statistical significance says nothing about the practical significance of such a difference.

It has been observed that preoccupation with sample size in studies overshadows the more pertinent concerns of elimination of bias, and that unbiased trials with imprecise results trump no results at all (Schulz and Grimes, Lancet 2005):

> "*Trials should be methodologically strong, thus eliminating bias. Unfortunately, the adequate-power mantra frequently overwhelms discussion on other methodological aspects, e.g. inadequate randomisation usually yields biased results which cannot be salvaged even if a huge sample size generates great precision. By contrast, if investigators design and implement a trial properly, that trial essentially yields an unbiased estimate of effect, even if it has lower power (and precision).*"

For 12 months Herceptin treatments, the "weight of evidence" argument is hampered by the possibly poorer quality of the relevant trials. This is where, for example, none of the three concurrent 12 month treatment trials have published their individual results in order to allow due scientific scrutiny and peer review, and hence we cannot be confident of their methodological quality (yet where the FinHer trial was adequately reported):

- It is difficult to assess the quality of two of the three trials (B31 and N9831) because publication has been limited to joint analyses. There has been little disaggregation into the separate studies or any description of key validity aspects of the separate studies as published. Yet the two studies' concurrent arm results for efficacy (but not cardiotoxicity, reported separately) have been published and presented as post-hoc pooled analyses that are limited to the concurrent treatment groups of the two studies that were of appreciably different design.[1]

  The methodologically robust approach would instead be to separately publish each trial's study design and methodology information and efficacy data, enabling adequate critical appraisal of each trial and the assessment of between-trial variability[2] in any meta-analysis that combined the results of the two trials.

[1] The N9831 and B31 trials of concurrent regimens in the Romond 2005 interim analysis 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)

[2] 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). http://www.hta.ac.uk/fullmono/mon1126.pdf Appendix 4 Statement from NICE DSU (Abrams K) (p 115).

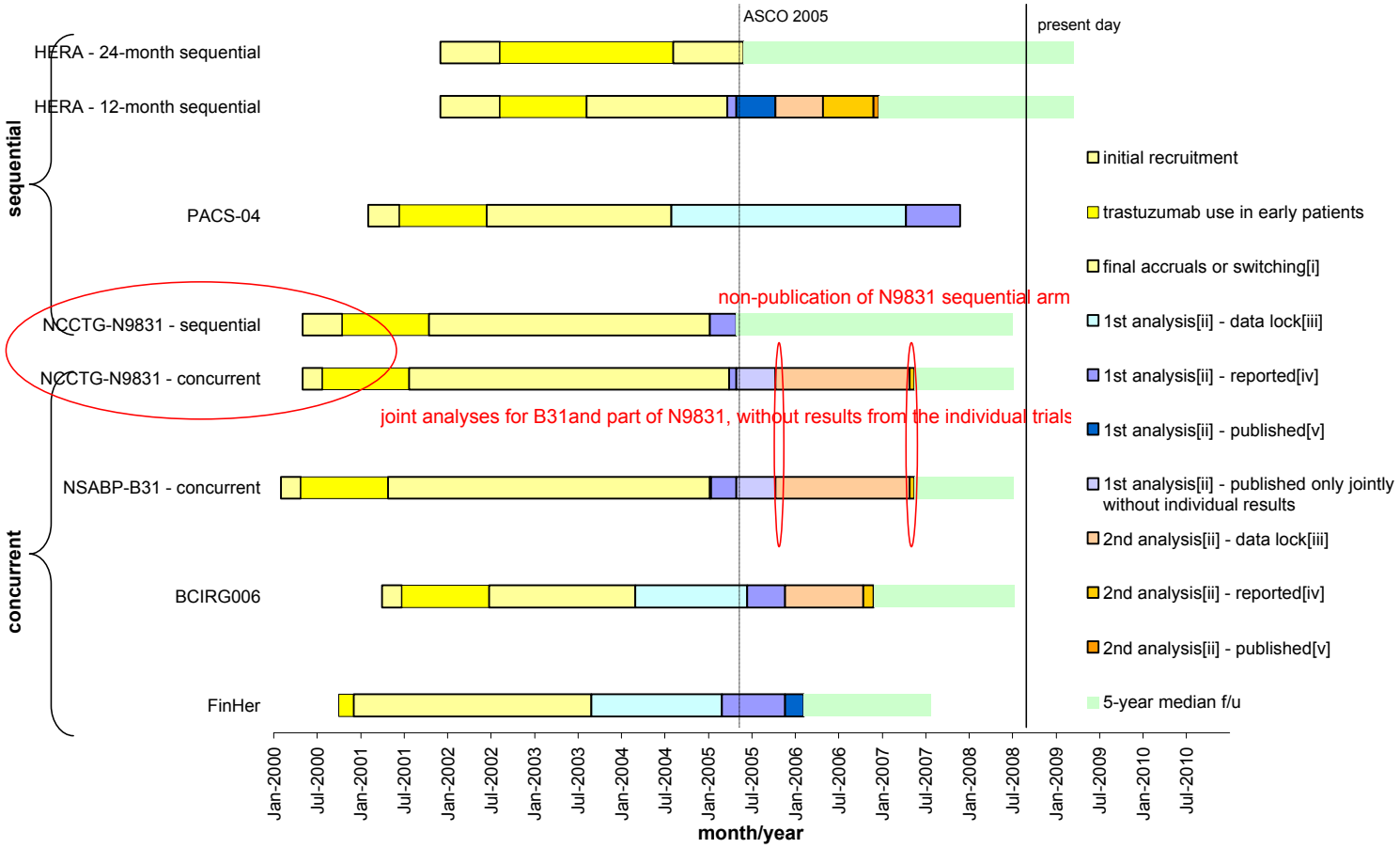
- For the other key trial of concurrent 12 month treatment, BCIRG006, reporting of its results are limited to conference slideshow presentations, making it difficult to assess its validity.

Furthermore, most trials do not report their allocation concealment methodology, i.e. the efforts to ensure the study investigators did not know ahead of time which patients were going to be assigned to what treatments. Such foreknowledge can introduce bias by inappropriately assigning 'winners' to believed-superior treatments. Inadequate or unclear allocation concealment may mean 30-40% larger estimates of treatment effects than is truly the case, which conceivably appreciably overstates results.

By contrast, FinHer is the only trial of all of the Herceptin trials that has published the results of all of its treatment arms individually and has adequately reported its methods for concealing allocation.

Adding to uncertainty, with all of the Herceptin trials aside from PACS04 (which has reported final results for its HER2 positive patients); only preliminary interim results have been reported. All the Herceptin trials aside from PACS04 continue to follow-up patients, where PACS04 alone has met its preset target event accruals. These features can be seen in the following diagram (Figure 4).

Figure 4. 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, NCCTG-N9831, NSABP-B31, FinHer, BCIRG006) 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 has reported final results for its HER2 positive patients, having met its preset target event accruals; these results 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

The optimal schedule and duration of treatment for Herceptin in the adjuvant treatment of early stage HER2-positive breast cancer cannot be determined from the current evidence. This is not unusual for a new treatment with emerging evidence. There are particular questions about the durability of benefit, and the scheduling in relation to chemotherapy.

PTAC considers that the Herceptin data are subject to unacceptable publication bias, that data should have been published, and their continued absence raises important

questions. PTAC has also restated that more clinical research is needed to see whether longer duration concurrent treatment is any better than short duration concurrent treatment, and the SOLD study may help answer this.

Detail of trials

Table 3 which follows details of the design and results of the six relevant trials that have reported disease outcomes for adjuvant trastuzumab compared with standard chemotherapy treatment alone in HER2-positive early breast cancer:

1. HERA[1 2]
2. PACS-04[4 5]
3. NCCTG-N9831[3 6 7]
4. NSABP-B31[6 7]
5. BCIRG 006[8]
6. FinHer[9]

In these studies, trastuzumab (Herceptin) was investigated in one of two broad treatment regimens (Figure 4):

1. 'sequential treatment'—trastuzumab for 12 months following completion of chemotherapy (anthracycline +/- taxane): HERA, NCCTG N9831 Arm B, PACS04;

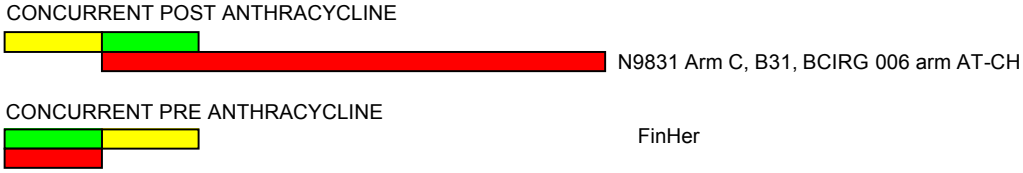
2. 'concurrent treatment'—trastuzumab for 9-10 weeks, or 12 months, started in combination with taxane chemotherapy (either preceding or following completion of anthracycline chemotherapy): NASBP B31, NCCTG N9831 Arm C, BCIRG 006, and FinHer.

Trastuzumab treatment regimens in these studies have varied in their association with taxanes (sequential to, concurrent with), duration of trastuzumab (between 9 weeks and 2 years), sequence relative to anthracycline chemotherapy (before or after), and dosing frequency (weekly or every three-weekly dosing) (Figure 5).

Figure 5. Anthracycline-containing treatment regimens in trials of trastuzumab in early stage HER2-positive breast cancer

1) Sequential

2) Concurrent



Key:

taxane chemotherapy

anthracycline-containing chemotherapy

trastuzumab

Broad schematic only. Other regimens, not illustrated, include concurrent use of trastuzumab with docetaxel and carboplatin chemotherapies in BCIRG 006 (no anthracycline chemotherapy), and 2 years' sequential trastuzumab (following anthracycline and then taxane chemotherapies) in HERA (no data available to date). HERA permitted the use of a variety of different combinations of chemotherapy, including non-anthracycline regimens using CMF (http://content.nejm.org/cgi/data/353/16/1659/DC1/1).

Specific treatment regimes studied in the trials were as follows:[3]

- HERA—a three-arm open-label RCT comparing 12 months and 24 months sequential with standard chemotherapy:
  - **control (n=1693-1698[4]):** *Observation alone following completion of standard neoadjuvant or adjuvant chemotherapy*
  - **1 Year arm (n=1694-1703[4]):** *12 months sequential trastuzumab treatment following completion of standard neoadjuvant or adjuvant chemotherapy*
  - **2 Year arm (n=1694-1701[4]):** *24 months sequential trastuzumab treatment following completion of standard neoadjuvant or adjuvant chemotherapy*
- PACS04—an open-label RCT comparing docetaxel/epirubicin with anthracycline treatment (FEC) for the adjuvant treatment of early stage breast cancer (n=3010). For the subset of women with HER2-positive cancers, patients were further randomised to two arms comparing concurrent trastuzumab (with either docetaxel/epirubicin or FEC) or FEC alone; note the distribution of patients between the other chemotherapy treatments (FEC100, ED) in the HER2 positive subpopulation has not been reported to date:

[3] Nearly all regimens have involved anthracycline chemotherapy, apart from BCIRG 006 which also included an arm that assessed concurrent trastuzumab with docetaxel and carboplatin (not anthracycline—Arm 'TCH', 1075 patients), and in HERA (which permitted a variety of chemotherapy regimens) where 6% of primary treatments contained no anthracyclines. Results from BCIRG 006 discussed here are therefore largely confined to the anthracycline-containing arms AC-T and AC-TH (control and added trastuzumab).

[4] Numbers of patients in the study arms reported in the HERA trial differ between the first (12 month median follow-up) and second (23 month median follow-up) interim publications of the trial (Piccart-Gebhart et al. NEJM 2005, Smith et al. Lancet 2007)

    - **Arm C docetaxel + epirubicin or FEC, no trastuzumab (n=268):** *6 cycles adjuvant 5-fluorouracil-epirubicin-cyclophosphamide, or 6 cycles concomitant epirubicin-docetaxel;*
    - **Arm D docetaxel + FEC, trastuzumab (n=260):** *6 cycles FEC100, or 6 cycles ED; trastuzumab for 1 year*
- NCCTG N9831—a three-arm open-label RCT comparing sequential and concurrent trastuzumab treatment with standard chemotherapy:
    - **Arm A (control) (n= 979):** *4 cycles of AC treatment followed by 12 weeks paclitaxel*
    - **Arm B (12 months sequential trastuzumab treatment) (n=985):** *4 cycles of AC treatment followed by 12 weeks paclitaxel and then 52 weeks trastuzumab*
    - **Arm C (12 months concurrent trastuzumab treatment) (n=840):** *4 cycles AC followed by 12 weeks paclitaxel; trastuzumab started on day 1 of paclitaxel and continued for 12 months*.
- NASBP B31—a two-arm open-label RCT comparing concurrent trastuzumab treatment with standard chemotherapy:
    - **Control (n=1024):** *4 cycles of AC treatment followed by 12 weeks paclitaxel*
    - **12 months concurrent trastuzumab treatment (n=1019):** *4 cycles AC followed by 12 weeks paclitaxel; trastuzumab started on day 1 of paclitaxel and continued for 12 months*
- BCIRG 006—a three-arm open-label RCT comparing concurrent trastuzumab treatment (with 2 different chemotherapy regimens) with standard chemotherapy:
    - **Arm AC-T (control) (n=1073):** *4 cycles of AC treatment followed by 4 cycles docetaxel*
    - **Arm AC-TH (12 months concurrent trastuzumab) (n=1074):** *4 cycles of AC treatment followed by 4 cycles docetaxel; trastuzumab started on day 1 of docetaxel and continued for 12 months*
    - **Arm TCH (12 months concurrent trastuzumab) (n=1075):** *6 cycles docetaxel and carboplatin; trastuzumab started on day 1 of docetaxel/carboplatin and continued for 12 months*
- FinHer—an open-label RCT comparing docetaxel with vinorelbine for the adjuvant treatment of early stage breast cancer (n=1010). For the subset of women with HER2-positive cancers, patients were further randomised to four arms comparing concurrent trastuzumab (with 2 different chemotherapy regimens—docetaxel or vinorelbine) with docetaxel or vinorelbine chemotherapy alone:
    - **docetaxel + FEC, no trastuzumab (n=58):** *3 cycles of docetaxel followed by 3 cycles of AC*
    - **docetaxel + FEC, trastuzumab (n=54):** *3 cycles of docetaxel followed by 3 cycles of AC; trastuzumab started on day 1 of docetaxel and continued for 9 weeks*
    - **vinorelbine + FEC, no trastuzumab (n=58):** *3 cycles of vinorelbine followed by 3 cycles of AC*
    - **vinorelbine + FEC, trastuzumab (n=62):** *3 cycles of vinorelbine followed by 3 cycles of AC; trastuzumab started on day 1 of vinorelbine and continued for 9 weeks*

Study designs and their treatment regimens are summarised further in Figure 5 and in Table 3 below.

References for the six trials:

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Table 2. Updated* trastuzumab (Herceptin) clinical trial summaries**

	Sequential treatment trials, long duration (12 month)[5] regimens			Concurrent treatment trials, long duration (12 month) regimens			Concurrent treatment trials with short duration regimens[6]
	HERA	**N9831 Arm B**	**PACS04[7]**	**B31[8]**	**N9831 Arm C[8]**	**BCIRG006[9]**	**FinHer**
Patient Numbers	Observation: 1,693 Trastuzumab (1 yr): 1,694 Trastuzumab (2 yr):[5] 1,694	Observation: 979 Trastuzumab: 985	Observation: 268 FEC100 – n/a ED – n/a Trastuzumab: 260 FEC100 – n/a ED – n/a	Observation: 1,024 Trastuzumab: 1,019	Observation: 979 Trastuzumab: 840	Observation: 1,073 Trastuzumab: 1,074	Observation: (116) vinorelbine – 58 docetaxel – 58 Trastuzumab: (116) docetaxel - 54 vinorelbine - 62
Intervention	1 loading dose (8mg/kg) trastuzumab, then 6mg/kg every 3 weeks for one year or two years	1 loading dose (4mg/kg), then 2mg/kg every week for 52 weeks	1 loading dose (8mg/kg), then 6mg/kg every 3 weeks for one year	1 loading dose (4mg/kg), then 2mg/kg every week for 52 weeks[8]	1 loading dose (4mg/kg), then 2mg/kg every week for 52 weeks[8]	1 loading dose (4mg/kg), then 2mg/kg every week for 52 weeks	9 infusions at 1 week intervals. First dose 4mg/kg, remaining doses 2mg/kg
Timing of treatment	Sequential (after completion of all chemotherapy – anthracycline chemotherapy[10] and taxane treatment[11])			Concurrent with taxane (paclitaxel), after completion of anthracycline chemotherapy			Concurrent with taxane (docetaxel), before anthracyclines[2]
Disease free survival (DFS) hazard ratio (HR) (95% confidence interval)	12-mth median follow-up (mfu): 0.54 (0.43-0.67) 23-mth mfu: 0.64 (0.54-0.76)	1.5-yr mfu: 0.87 (0.67-1.13)	4-yr mfu: 0.86 (0.61-1.22)	2.4-yr mfu: 0.45 (0.35-0.58) 3.3-yr mfu: Not reported (joint analysis with N9831 = 0.49 (0.40-0.58) at 2.9 yr mfu)[8]	1.5-yr mfu: 0.55 (0.38-0.76) 2.4-yr mfu: Not reported (joint analysis with B31 = 0.49 (0.40-0.58) at 2.9-yr mfu)[8]	23-mth mfu: 0.49 (0.37-0.79) 36-mth mfu: 0.61 (0.48-0.76)	36-mth mfu: 0.42 (0.21-0.83)
Overall DFS HR (95% CI)	0.72 (0.67-0.78) (2-yr HERA f/u)			0.53 (0.46-0.60) (3-yr BCIRG006 f/u, 2.9-yr joint B31/N9831 f/u)			0.42 (0.21.0.83)
Overall survival (OS) HR (95% CI)	12-mth mfu: 0.76 (0.47-1.23) 23-mth mfu: 0.66 (0.47-0.91)	1.5-yr mfu: 0.85 (0.55-1.33)	4-yr mfu: 2.06 (0.61-6.99)	Not reported (joint analysis with N9831= 0.67 (0.48-0.93) at 2.0-yr mfu, 0.63 (0.49-0.81) at 2.9-yr mfu)[8]	Not reported (joint analysis with B31= 0.67 (0.48-0.93) at 2.0-yr mfu, 0.63 (0.49-0.81) at 2.9-yr mfu)[8]	36-mth mfu: 0.59 (0.42-0.85)	36-mth mfu: 0.41 (0.16-1.08)
Overall OS HR (95% CI)	0.76 (0.65-0.88)			0.63 (0.51-0.77)			0.41 (0.16-1.08)

*New information since April 2007 is indicated by red text.

**The six RCTs reporting disease outcomes for adjuvant trastuzumab compared with standard chemotherapy treatment alone in HER2-positive early breast cancer

[5] No data have yet been reported for the outcomes of the 2 year trastuzumab treatment arm in the HERA trial.

[6] 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.

[7] The randomisation of patients to trastuzumab in PACS04 was a second randomisation applied specifically to the HER2 positive subpopulation (n=528 randomised). All patients in this trial (total n=3010) were initially randomised to receive either Arm A: 6 cycles of adjuvant 5-fluorouracil-epirubicin-cyclophosphamide (FEC100: F and C 500 mg/m^2, E 100 mg/m^2), or Arm B: 6 cycles of concomitant ED (E and D 75 mg/m^2) every 3 weeks. As soon as HER2 status was available, patients with HER2 positive tumours were randomised to Arm C: additional observation only, or Arm D: additional 1 year of trastuzumab (T) (8 mg/kg loading dose, 6 mg/kg 3qw). The primary endpoint was 3-year DFS for the C and D arms. The distribution of patients between the other chemotherapy treatments (FEC100, ED) in the HER2 positive subpopulation is not available.

[8] Although reported jointly, the NSABP-B31 and NCCTG- N9831 trials of concurrent regimens 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 started to be used in the trials; recommendations for post surgical radiotherapy; and primary endpoints (N9831 DFS, B31 OS).

[9] Note that there was also an arm to BCIRG006 ('arm TCH') that consisted of 6 cycles of docetaxel and carboplatin with concurrent trastuzumab (i.e. no anthracycline chemotherapy). However, because this regimen is not comparable to the other regimens, these results are not presented in this table. For further information regarding BCIRG006 see TAR 75 Appendix One: Minutes of the relevant clinical advisory committee meetings.

[10] Anthracycline containing chemotherapy regimens (FEC or FAC).

[11] The HERA trial allowed several different chemotherapy regimens.