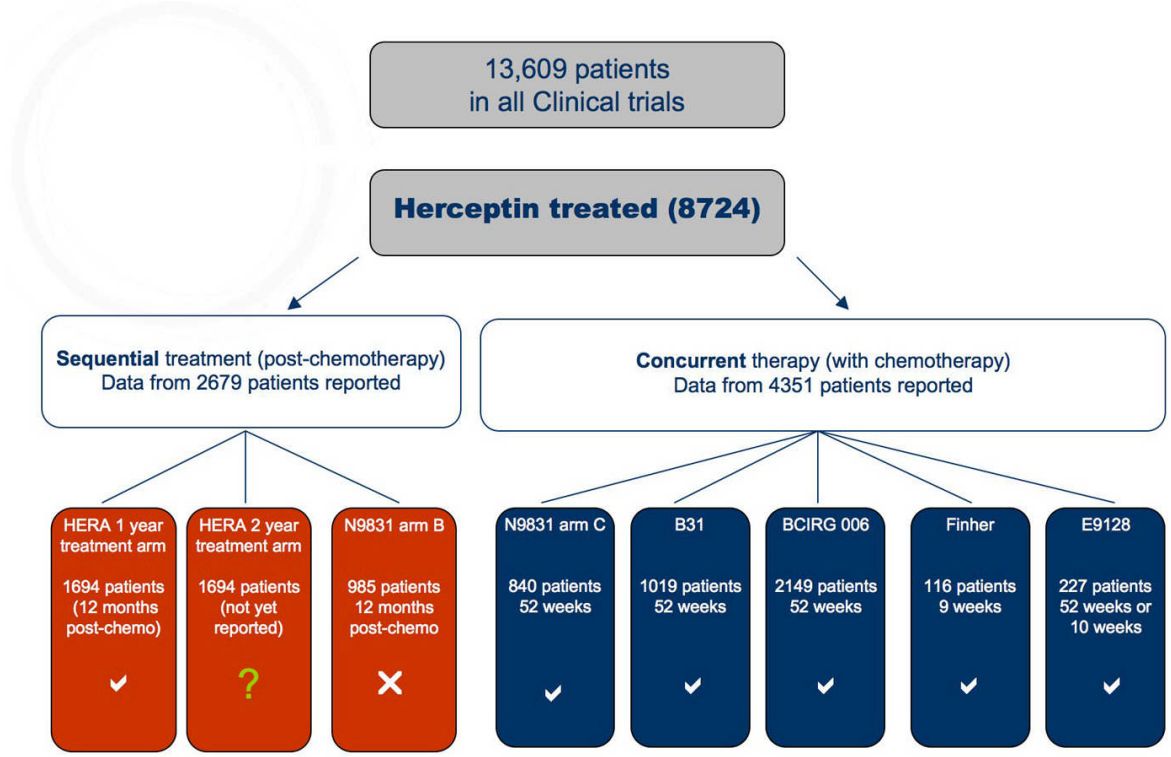
Appendix Six:

Clinical data

1. Efficacy of sequential and concurrent treatments



Key to graphic:
√ statistically significant improvement in disease-free survival (DFS)
× no statistically significant improvement in DFS
? results awaited

2. Treatment regimens and available trial data

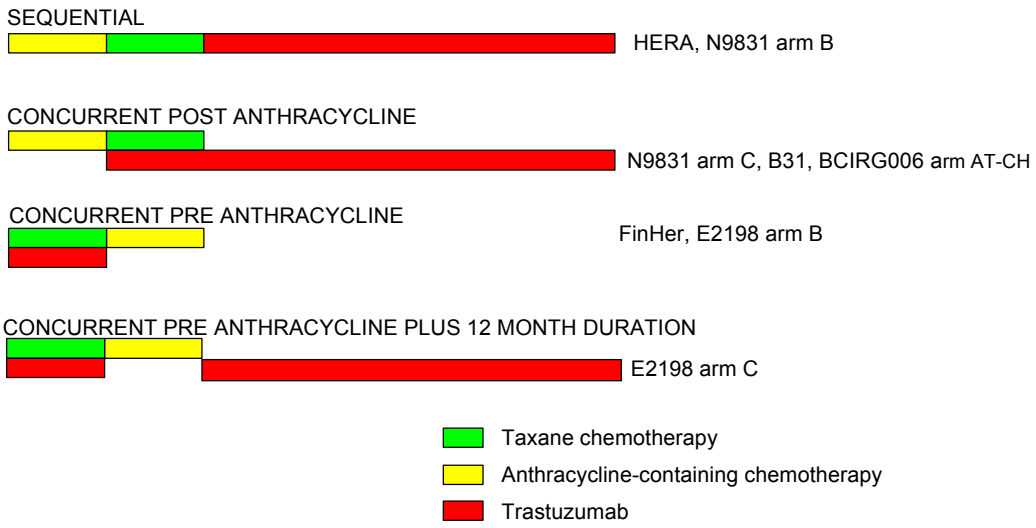
To date, adjuvant treatment of HER2+ breast cancer with trastuzumab has been investigated in three broad treatment regimens (see figure below):

1. trastuzumab for 12 months following completion of chemotherapy (anthracycline +/- taxane) ('sequential treatment')

2. trastuzumab for 12 months started in combination with chemotherapy (taxane) following completion of anthracycline ('concurrent treatment post-anthracycline')

3. trastuzumab started in combination with chemotherapy (with a taxane) and completed prior to anthracycline treatment (total duration of 9–10 weeks) ('concurrent treatment pre-anthracycline').

Figure. Published study treatment regimens of trastuzumab in early breast cancer



There have been five open-label randomised trials reporting to date outcomes for adjuvant trastuzumab against standard treatment in early stage breast cancer[1] – HERA[2 3], NASBP B31[4], NCCTG N9831[4 5], BCIRG006[6], and FinHer.[7]

Questions remain over the extent that sequential treatment prevents recurrence in the short and long term, and the optimal schedule and duration of treatment for trastuzumab in the adjuvant treatment of breast cancer cannot be determined from the current evidence.[8] This is not unusual for a new treatment with emerging evidence. Combinations of trastuzumab with chemotherapy seem to have a synergistic effect in both adjuvant treatment and treatment of metastatic disease.[9]

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[1] Identified in: Belgian Health Care Knowledge Centre (KCE). Trastuzumab in early stage breast cancer. KCE reports vol. 34C, 2006. http://kce.fgov.be/index_en.aspx?ID=0&SGREF=5211&CREF=7198

[2] Piccart-Gebhart M.J. Procter M, Leyland-Jones B. et al., Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. N Engl J Med 2005;353(16):1659-1672. http://content.nejm.org/cgi/content/full/353/16/1659

[3] Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A. *et al.* 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

[4] 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(16):1659-1672. http://content.nejm.org/cgi/content/full/353/16/1673

[5] Perez EA. Further Analysis of NCCTG-N9831. Slide presentation ASCO annual meeting 2005, available online at http://www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005815-00_21-001,00.asp

[6] Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, 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/eqkdodg2dy7t557o7s6uvj7ytpe6gcfg5gmh2ely6hnhh5pjlabz3nd6jddlnao7qoikej3edohsijyiisfvp367uuc/BCIRG006+2nd+Interim+Analysis.pdf

[7] 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(8):809-20. http://content.nejm.org/cgi/content/full/354/8/809

[8] Hind D, Pilgrim H, Ward S. Questions about adjuvant trastuzumab still remain. Lancet 2007; 369:3-5. http://www.thelancet.com/journals/lancet/article/PIIS014067360760004X/fulltext

[9] Hypothetically, all (or almost all) breast cancer cells need to be eradicated for cure. Concomitant administration of the most effective agents available is an obvious strategy to achieve complete eradication of all subclinical cancer. Based on in vitro data, the combination of trastuzumab and docetaxel may be one of the most synergistic ones of all the trastuzumab combinations available to

However, evidence is available that raises questions about the place of 12-month sequential therapy as the standard-of-care recommended by the supplier in its datasheet (in NZ the approved indication is restricted to the HERA regimen, unlike Australia and the US). Particular questions are raised about the durability of benefit, and the scheduling in relation to chemotherapy.

PHARMAC (and other international bodies such as NICE in the UK) had been asked to make decisions on funding 12-months of sequential trastuzumab on the basis of 12-month median follow-up data from the HERA study (i.e. the sequential treatment regimen). This was supported with longer-term follow-up data from the BCIRG006 and combined results of the NSABP B31 and N9831 studies (concurrent treatment).

However, N9831 investigated both sequential and concurrent treatment with trastuzumab.[10] Separate data each of these arms of the N9831 arms are available in an unpublicised slide presentation of an unplanned interim analysis presented at ASCO in 2005. The separation of the data for sequential treatment from the concurrent treatment, albeit unpublished, is important as it raises questions about optimal treatment scheduling in relation to chemotherapy.

N9831 demonstrated a large and significant benefit in disease-free survival (DFS) over usual care with one year of trastuzumab administered concurrently with taxane chemotherapy (HR 0.48, 95% CI 0.39-0.59). N9831 did not however show a statistically significant improvement in DFS when trastuzumab was administered after completion of all chemotherapy (arm B, sequential therapy), as compared with the control arm (arm A) (HR 0.87, 0.67-1.13). This sequential regimen is the same as used in the HERA trial, and is approved by Medsafe in New Zealand (NZ datasheet).

At its May 2006 meeting, PTAC considered the above unpublished disease-free survival data for N9831, supplied in the form of MS PowerPoint slides of the conference presentation. Members noted that sequential trastuzumab treatment (arm B) was not statistically superior to non-trastuzumab treatment (arm A), but that concurrent trastuzumab treatment (arm C) resulted in a significant improvement in disease-free survival compared with arm B. Members considered that although these data were preliminary, they raised concerns about the optimal dosing schedule of trastuzumab treatment. PTAC requested that the supplier provide full data from the N9831 trial.

Although the HERA study of sequential treatment came to a different result than the sequential arm of N9831, the conflicting information from these studies raises questions about the effectiveness and duration of response to sequential trastuzumab. This is particularly so in light of the 2-year median follow-up data from HERA. The 2-year f/u HERA results reported a statistically significant improvement in overall survival[11], but at the same time showed reduced benefit in disease-free survival.[12]

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date. These in vitro findings are supported by the clinical data suggesting high activity of the docetaxel plus trastuzumab regimen in the adjuvant, preoperative systemic, and metastatic setting. Long duration of adjuvant administration of single-agent trastuzumab might also result in cancer cell eradication and gradual death of dormant cancer cell populations, although the bulk of evidence suggests that trastuzumab administered in combination with chemotherapy is more effective that trastuzumab given as a single agent. (Joensuu – SOLD protocol)

[10] ***N9831 trial:***

Arm A (control): *4 cycles of AC treatment followed by 12 weeks paclitaxel*

Arm B (post-anthracycline and sequential with trastuzumab treatment): *4 cycles of AC treatment followed by 12 weeks paclitaxel and then 52 weeks trastuzumab*

Arm C (post-anthracycline and concurrent with trastuzumab treatment): 4 cycles AC followed by 12 weeks paclitaxel with trastuzumab, and a further 40 weeks trastuzumab

[11] HERA's previous 12-month median f/u results for overall survival (Piccart-Gebhart et al 2005) did not reached statistical significance. Advocates for the HERA regimen (Hortobagyi 2005) relied instead on extrapolating from the Romond overall survival results.

[12] In HERA, by 2 years the risk reduction in DFS for patients who had been treated with trastuzumab had reduced from what had been reported in the 12-month median f/u HERA publication. The HERA disease-free survival 12-month median f/u hazard ratio was 0.54 (95% CI 0.43-0.67) (Piccart-Gebhart et al 2005); 2-year median f/u HR 0.64 (0.54-0.76) (Smith et al 2007).

Including the interim N9831 arm B data and updating the HERA results for the 2-year median data means that effects of sequential treatment on disease progression reduces by one third – the hazard ratio increases from 0.54 (95% CI 0.43-0.67) for the HERA 12-month median follow-up data to 0.70 (0.61-0.81) for the pooled HERA median 2-year follow-up and N9831 arm B data.

However, the results for N9831 arm B were an unplanned interim analysis with low statistical power, and longer follow-up is needed for confirmation.[3] PTAC (February 2007) considered that there was now likely to be longer-term follow-up of outcomes (disease free survival and mortality) in this study, and asked for all the updated data from all three arms of the trial be made available.

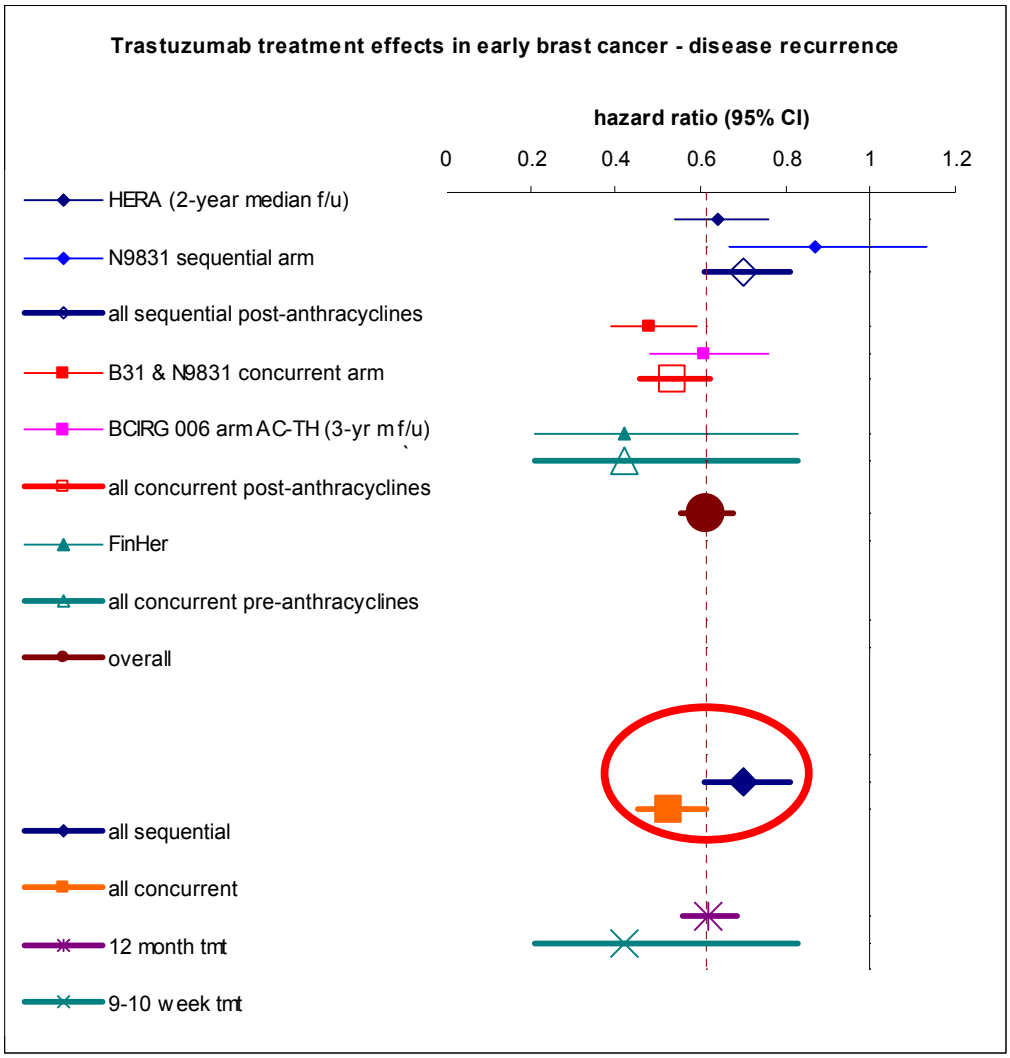
Yet despite small numbers of events, the N9831 trial showed a statistically significant benefit of concurrent therapy over sequential therapy for disease progression (HR 0.64, 2P logrank 0.0114), although this finding is qualified.[13] By way of confirmation another large study of concurrent treatment, BCIRG006, also demonstrated a benefit after median 3 years of follow-up. Note however that the concurrent arm of N9831 also had a high incidence of cardiovascular events than the sequential arm (with similar caveats to the efficacy data[13]).

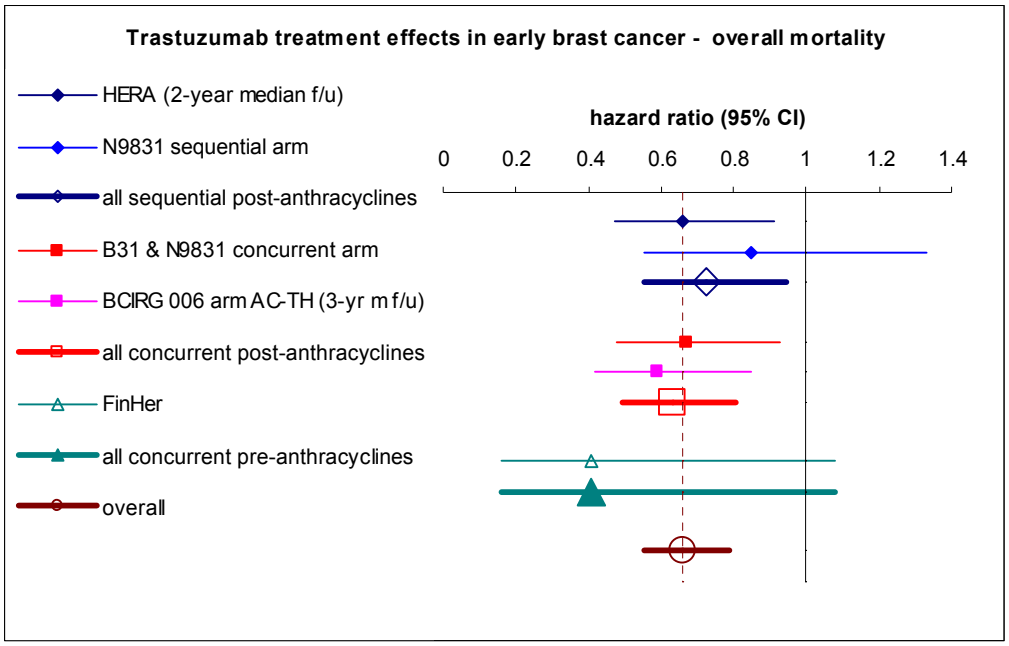
Results for both disease free survival and overall survival for all trials, and pooled results for regimens, can be seen in the following table and two figures.

[13] Note however with this comparison (N9831 arms B and C) that the median duration of trastuzumab treatment was likely to be longer in the concurrent arm (C) than the sequential arm (B). This was due to the different timing of trastuzumab sequencing, with the sequential arm commencing trastuzumab 12 weeks later. Hence patients in the concurrent arm were exposed to higher cumulative doses of trastuzumab at the time of the interim analysis – which may have contributed to both the concurrent arm's apparent improved disease progression and higher cardiotoxicity.

Trial	Sequential (trastuzumab post taxane) n tmt/N tmt vs. n obs/N obs, hazard ratio (95% CI)	Concurrent (trastuzumab with taxane) n tmt/N tmt vs. n obs/N obs, hazard ratio (95% CI)
(HERA 1 year f/up–interim result)	127/1694 vs. 220/1693, HR 0.54 (0.43-0.67)	
HERA 2 year f/up	218/1703 vs. 321/1698, HR 0.64 (0.54-0.76)	
NSABP B31		*83/864 vs. 171/872,* *HR 0.45 (CI not reported; 2P=10^{-9})*
NCCTG N9831	103/985 vs. 117/979, HR 0.87 (0.67-1.13)	*50/808 vs. 90/807,* *HR 0.55 (CI not reported; 2P=0.0004)*
joint analysis of N9831/B31		134/1217 vs. 261/1162, HR 0.48 (0.39-0.59)
BCIRG006 arm AC-TH (3 year f/u)		128/1074 vs. 192/1073, HR 0.61 (0.48-0.76)
Overall post-anthracycline treatment	321/2688 vs. 438/2677, ***HR 0.70 (0.61-0.81)***	262/2291 vs. 453/2235, ***HR 0.53 (0.46-0.62)***
FinHer (pre-anthracycline treatment)		12/115 vs. 27/116, HR 0.42 (0.21-0.83)
Overall, all regimens	595/5094 vs. 918/5028, **HR 0.61 (0.55-0.68)**	

Note: The hazard ratio for sequential treatment comprises the N9831 sequential (B) and HERA trastuzumab arms compared with respective control groups (HERA 2-year median follow-up results). The hazard ratio for concurrent treatment comprises N9831 concurrent (C), NSABP B31 trastuzumab and BCIRG006 AC-TH arms compared with respective control groups. The HR for concurrent trastuzumab is for post-anthracyclines, and hence does not include concurrent treatment given in FinHer (pre-anthracyclines).

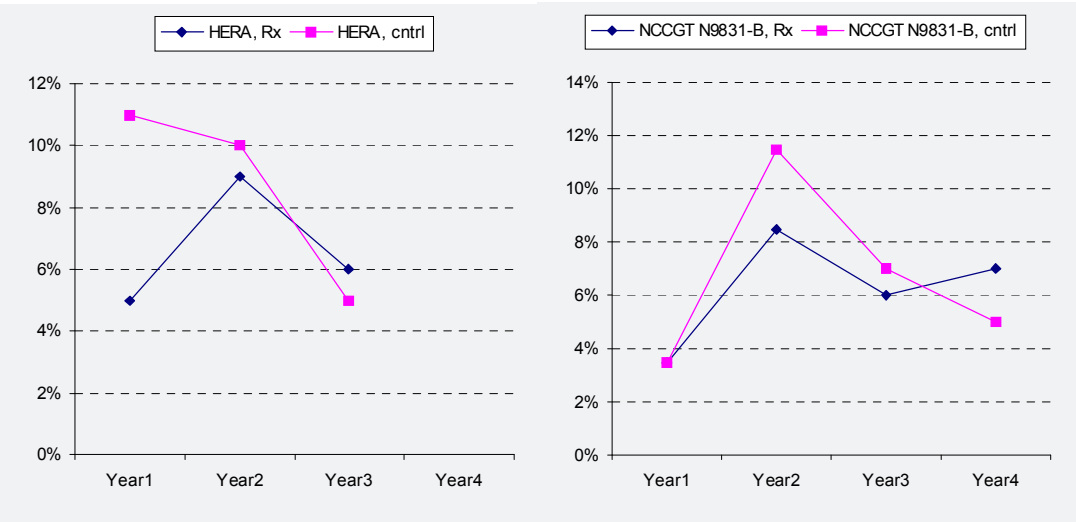

Trastuzumab treatment effects in early brast cancer - disease recurrence
hazard ratio (95% CI)
0
0.2
0.4
0.6
0.8
1
1.2
HERA (2-year median f/u)
N9831 sequential arm
all sequential post-anthracyclines
B31 & N9831 concurrent arm
BCIRG 006 arm AC-TH (3-yr m f/u)
all concurrent post-anthracyclines
FinHer
all concurrent pre-anthracyclines
overall
all sequential
all concurrent
12 month tmt
9-10 week tmt


Trastuzumab treatment effects in early brast cancer - overall mortality
HERA (2-year median f/u)
N9831 sequential arm
all sequential post-anthracyclines
B31 & N9831 concurrent arm
BCIRG 006 arm AC-TH (3-yr m f/u)
all concurrent post-anthracyclines
FinHer
all concurrent pre-anthracyclines
overall
hazard ratio (95% CI)
0
0.2
0.4
0.6
0.8
1
1.2
1.4

3. Durability of response

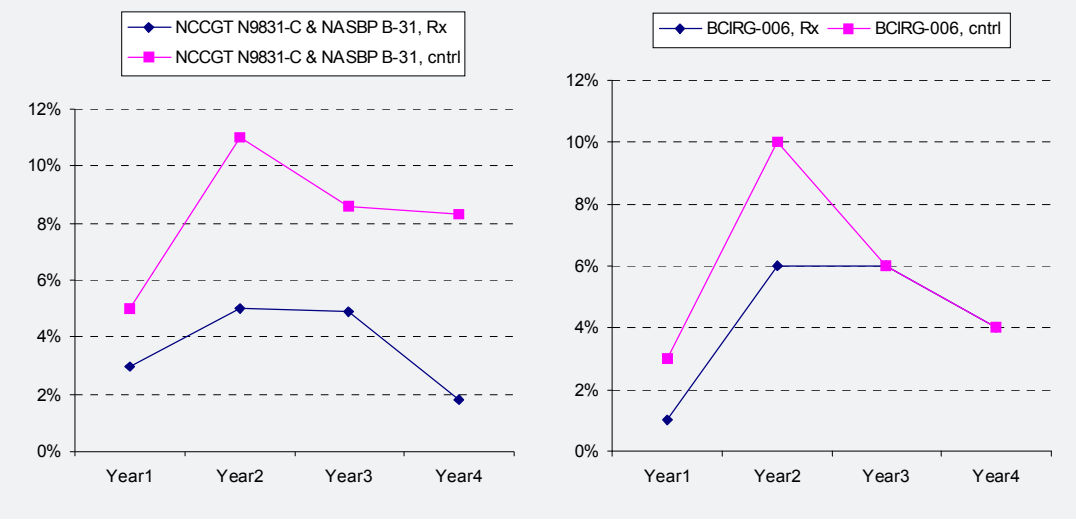
The durability of response of sequential therapy has not been demonstrated, and extended follow-up on the HERA study may not answer this question due to partial loss of the control arm (following one year, patients were able to cross over to the treatment arm in a non-randomised fashion). The 2-year follow-up HERA results showed reduced benefit in disease-free survival, when the interim analysis (Piccart-Gebhart et al 2005) reported a disease-free survival hazard ratio over 12-months' median follow-up of 0.54 (95% CI 0.43-0.67), but the 2-year median follow-up data (Smith et al 2007) showed a HR of 0.64 (0.54-0.76).

For sequential regimens, the data suggest convergence in rates by 3 years, i.e. trastuzumab no longer has any effects on disease events. For concurrent regimens, the data suggest a mixture of continuing divergence and some convergence by 4 years – see the following graphs comparing death or relapse rates per year for trastuzumab versus standard treatment in the five trials.



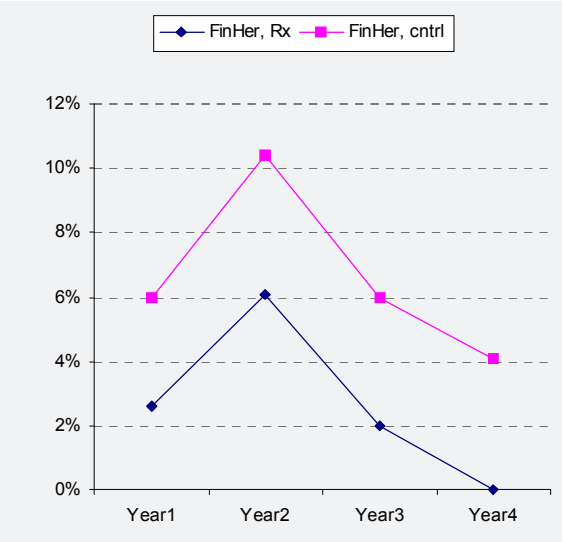
HERA

N9831 arm B vs. arm A



Joint analysis N9831 arm C vs. arm A, B31 (Romond)

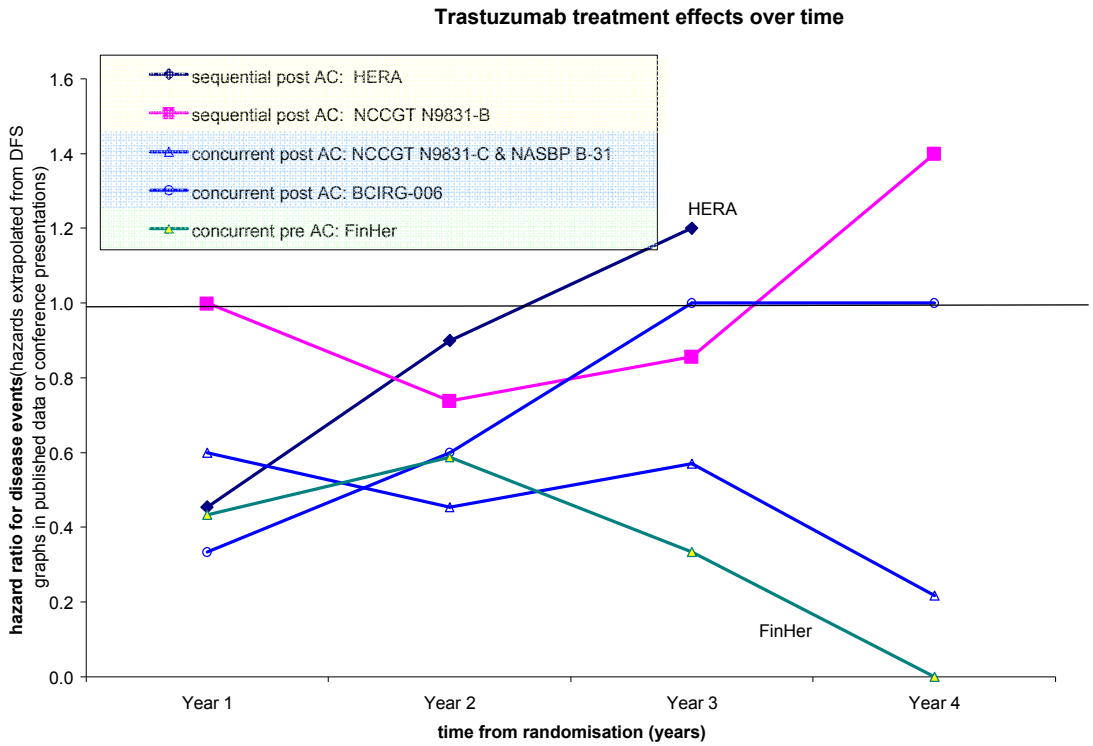
BCIRG 006



FinHer

These results must however be treated with caution, given the small numbers of patients and events as time progresses (and hence instability with greater uncertainty in the later years).

Using the above data, the following figure shows changes in hazard ratios over time for relevant trials, calculated from the published etc. DFS survival graphs. This suggests apparent waning of effects with HERA, also for N9831 arm B (sequential) and BCIRG 006 (concurrent), but not for other concurrent regimens (B31/N9831 arm C joint analysis, FinHer).



4. Cardiotoxicity

All three studies of concurrent treatment (BCIRG006, N9831 and B31) used a regimen of trastuzumab administered concurrently with a taxane in addition to extended (up to 12 months) treatment on completion of anthracycline-containing chemotherapy. Anthracycline treatment has a dose-related cardiotoxic effect on the heart, and as a result 15-20% more patients will not meet the cardiac criteria required for trastuzumab treatment initiation if trastuzumab is initiated after patients receive cardiotoxic anthracycline treatment.[14]

The concurrent treatment regimens used in N9831 (arm C) and NSABP B31 (i.e. anthracycline chemotherapy followed by 12 months trastuzumab started concurrently with a taxane) demonstrated a higher risk of cardiotoxicity than the sequential treatment arms (HERA and Arm B of N9831). The pooled analysis of N9831 and NSABP B31 (Romond 2005) reported that 14.2% of trastuzumab treated patients discontinued treatment before 52 weeks because of a confirmed asymptomatic decline in LVEF. Another 4.7% discontinued because of symptoms of CHF or another adverse cardiac effect. In addition, 30.5% of patients required at least one trastuzumab dose delay in because of a decrease in LVEF or cardiac symptoms. The cumulative incidence for NYHA class 3 or 4 CHF/death from cardiac causes at 3 years was 0.8% and 0% in control group, 4.1% and 2.9% in the trastuzumab group.

The above information suggests that, although more efficacious than 12 month sequential treatment (overall HR for DFS = 0.49 compared with HR = 0.66 for sequential), the 12 month concurrent regimen (post anthracycline) is less safe for patients because of the associated risk of cardiotoxicity.

5. Concurrent treatment pre-anthracyclines (FinHer and E2198)

FinHer

FinHer is an open-label RCT that is comparing docetaxel with vionorelbine for the adjuvant treatment of early stage breast cancer (n=1101), where women with HER2 positive cancers have been also assigned to receive nine weeks concomitant treatment with trastuzumab or no such treatment (n=232). Results to date, as were reported in the NEJM in 2005, have in fact been a pre-planned early interim analysis, pending final analysis at five years median follow-up (or 150 events overall, whichever occurring earlier). Data from final analysis may be available from mid-2007 (where the early efficacy analysis (NEJM 2005) was for when median follow-up exceed three years and was able to take place in May 2005) (Joensuu et al NEJM 2006).[15]

The efficacy results of the FinHer trial to date suggest that concomitant administration of trastuzumab with a taxane is effective in the treatment of HER2-positive early breast cancer. Trastuzumab was administered weekly concomitantly either with 3-weekly docetaxel or weekly vinorelbine, followed by 3 cycles of FEC in each arm. Docetaxel improved recurrence-free survival as compared to vinorelbine (hazard ratio 0.58, 95% CI 0.40 to 0.85), and trastuzumab improved recurrence-free survival as compared to the same chemotherapy administered without trastuzumab (hazard ratio 0.42, 95% CI 0.21 to 0.83). During a median

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[14] Belgian Health Care Knowledge Centre (KCE). Trastuzumab in early stage breast cancer. KCE reports vol. 34C, 2006. http://kce.fgov.be/index_en.aspx?ID=0&SGREF=5211&CREF=7198. pp 51, 72.

[15] FinHer study was designed to have a power of 0.80 to detect an increase in five-year recurrence-free survival from 70 percent to 80 percent in the docetaxel-plus-FEC group as compared with the vinorelbine-plus-FEC group (with use of a twosided test at a significance level of 0.05); approximately 150 events were required for this purpose. The study's designers estimated at the time that 30% of the participants would have breast cancer with HER2/neu amplification and that the study would be able to detect a difference in their five-year recurrence-free survival of 50 percent to 67 percent at a power of 0.80 when approximately 1000 patients were enrolled. Protocol-defined safety analyses took place in March 2001, September 2001, and December 2002. The protocol specified that safety and early efficacy analyses were to be carried out when the median follow-up time exceeded three years; this point was reached in May 2005, hence the NEJM paper published in February 2005. The final analyses is scheduled to be performed when 150 events have occurred or the median follow-up time exceeds five years. For the primary variable, a P value of less than 0.029 was considered to indicate significance, in order to maintain an overall type 1 error of 0.05 for the interim and final analysis.

follow-up time of 3 years reported to date, these treatments were not associated with detectable cardiac toxicity, although caution is required with this interpretation.[16]

Note however that the above estimates of efficacy in this early analysis may reduce once final analysis has been completed, as has occurred with the HERA trial and similar to interim efficacy analyses elsewhere showing perhaps "implausibly large treatment effects".[17]

The data to date suggest that the combination of docetaxel plus 9-week concomitant trastuzumab is effective and well tolerated in the treatment of HER2-positive breast cancer. However, the subgroup of the study that evaluated adjuvant trastuzumab was small, with 232 patients randomized to receive or not to receive trastuzumab, and overall survival (OS) reported to date has not been statistically significant. These two issues are addressed as follows:

1. Patient numbers

   In terms of patient numbers in the FinHer trial (the 95% was CI 0.21-0.83, which reflected the degree of uncertainty from small numbers), the trial was able to give results that were statistically significant despite its smaller size. This reflects the strong efficacy of short duration reverse-order concurrent treatment in this setting (more than halving disease recurrence), so that fewer patients were needed to confirm such a strong effect. HER2 +ve patients studied in FinHer could have been as few as 145 for the results to still be statistically significant (calculated using binomial methods using constant relative risk).[18]

   In addition, similar scrutiny to study size and effects can also apply to the HERA and other sequential data (being the previous regimen strongly advocated for). Combining HERA 2-year follow-up and N9831 Arm B data reduces effectiveness by 1/3rd to reach a HR for 12 months' sequential treatment of 0.70 (0.61-0.81); the upper CI for this hazard ratio is similar to FinHer's:

   - Historically (and the basis for funding decisions elsewhere for 12 months' sequential trastuzumab treatment), HERA's interim hazard ratio (HR) was 0.54 (95% CI 0.43-0.67);
   - However, the combined updated HERA/N9831-B HR increases the hazard ratio for sequential treatment to **0.70** (0.61-**0.81**), thus a relative hazard reduction (RHR) of **30%** (**19%**-39%);
   - This compares with the FinHer HR of **0.42** (95% CI 0.21-**0.83**), being a RHR of **58%** (95% CI **17%**-79%).

   Hence, the most realistic estimates suggest the FinHer regimen should be at least as effective as sequential regimens (RHR 58% vs. 30%), and at the very worst , even accounting for its smaller number of patients, the FinHer results were nearly as effective as sequential regimens (17% vs. 19%) – see graph below.

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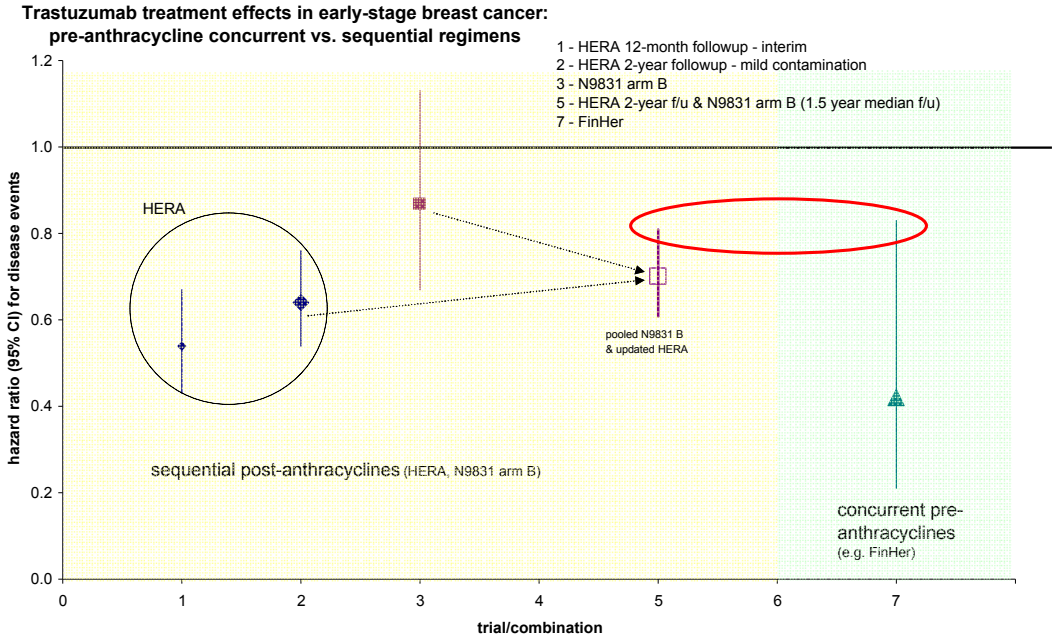
[16] The low cardiotoxicity observed in FinHer could also be explained by the relatively low cumulative dose of anthracycline chemotherapy (180 mg/m2 epirubicin while the maximum tolerated cumulative dose of epirubicin is of 720mg/m2). In the B31/N9831 studies doxorubicin was administered at a cumulative dose of 240 mg/m2 while its maximum tolerated cumulative dose is only 500 mg/m2. Epirubicin is generally presented as a less cardiotoxic agent than doxorubucin. Indeed, as stated in the FinHer paper, the small size and the short duration of the follow-up are limitations of the study and the optimal duration of adjuvant trastuzumab therapy is not known and may be clarified only in further randomized trials. (KCE 2006)

[17] Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, et al. Randomized trials stopped early for benefit: a systematic review. JAMA. 2005 Nov 2;294(17):2203-9.

[18] By contrast, in order for HERA to achieve its HR of 0.64 at the 23 month median follow-up, a minimum of around 560-570 patents would have been required (HERA did so with its 3,401 patients, because it was powered to detect changes in overall survival, hence its narrower CI for DFS, albeit with lessened efficacy for point estimates than seen with FinHer.



2. Overall survival

As stated above, the FinHer results as reported to date have not as yet confirmed benefits in terms of overall survival. At three years median follow up, the overall survival (OS) benefit in the treatment arm compared with the status quo was not statistically significant (HR = 0.41, 0.16-1.08).

It should be noted however, that this non-significant overall survival result may result from the combination of the small sample size and shortened follow-up at the time of analysis; as noted above, the trial results as reported in the NEJM in 2005 were a pre-planned early interim analysis, pending final analysis at five years median follow-up (or 150 events overall, whichever occurring earlier).[19]

Given the trend to a strong effect on OS (the 0.41 HR), then speculatively this trend may have become statistically significant within 3 years and 8 months median follow-up (calculated using binomial methods using constant relative risk of 0.43), i.e. by around January 2004. Although this may be an underestimate (given for instance the improved baseline survival seen in out years elsewhere), it still seems likely that, based on the trend in OS seen in the early efficacy FinHer results, a statistically significant improvement in OS may become evident in the final 5-year median follow-up analysis of FinHer later in 2007.

PTAC considered that the number of patients treated in the FinHer study was significant and that the data from that trial were valuable.

Possible synergism of docetaxel with trastuzumab

The FinHer study was conducted on the hypothesis that the issues of cardiotoxicity may be better managed when trastuzumab treatment is given concurrently with taxanes but prior to cardiotoxic anthracycline

[19] Data from final analysis may be available from mid-2007 (where the early efficacy analysis (NEJM 2005) was for when median follow-up exceed three years and was able to take place in May 2005) (Joensuu et al NEJM 2006

chemotherapy, [20] and on data available in metastatic disease that indicated a synergistic effect of trastuzumab when given in combination with chemotherapy (note that this synergism hypothesis has subsequently been supported by N9831 comparison of sequential vs. concurrent).

A major aim of FinHer was to determine which is the most effective treatment – vinorelbine or docetaxel – in early stage breast cancer (with and without HER2 amplification). In patients that did and did not have HER2 amplification (i.e. all patients), docetaxel had better effects on disease progression – the HR for DFS favoured docetaxel over vinorelbine (HR 0.58 (0.4-0.85)). The total patient numbers initiating treatment in this study were 507 using vinorelbine and 502 on docetaxel. OS was in favour of docetaxel, but this was not statistically significant (HR 0.66 (0.38-1.17)).

The HER2 positive docetaxel group did not undergo a prospectively-defined subgroup analysis. However, informal post-hoc analysis of the trastuzumab (HER-2 positive) patients who were treated with docetaxel and trastuzumab gives a relative risk for disease recurrence of 0.27 (0.08-0.90) – where docetaxel + FEC + trastuzumab vs. docetaxel +FEC + no trastuzumab = 3/54 vs. 12/58 events/patients = 5.6% vs. 20.7%; this compares with a worse and statistically non-significant result for vinorelbine + FEC patients in FinHer (RR for trastuzumab vs. no trastuzumab of 0.57 (0.27-1.20). However, this is a small, retrospectively -defined post-hoc subgroup analysis with no evidence of statistical heterogeneity on formal testing, and as such the results should be treated with caution.

Yet although such results are fraught with 'data-snooping' and cannot be validly extrapolated to estimate expected results in clinical practice, it does support the hypothesis that docetaxel and trastuzumab may have a synergistic effect when they are used together as per the FinHer regimen and that the real-life risk reductions are likely to be more if anything than seen with sequential 12 month treatment.

E2198

A second-study (E2198[21]) of short-duration trastuzumab therapy given concurrently with paclitaxel was presented as a poster at ASCO 2006. This study compared short duration trastuzumab (10 weeks) given concurrently with paclitaxel prior to anthracycline treatment, with the same treatment plus an additional 52 weeks trastuzumab after completion of anthracycline treatment. The 5-year follow-up reported similar clinical outcomes from the short duration concurrent regimen as with extended (12 month) trastuzumab treatment. [22]

Although the study did not set out to determine efficacy, and was not powered to determine equivalence, the results lend weight to the case for efficacy of short duration concurrent trastuzumab therapy before anthracycline containing chemotherapy.

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[20] Hypothetically, all (or almost all) breast cancer cells need to be eradicated for cure. Concomitant administration of the most effective agents available is an obvious strategy to achieve complete eradication of all subclinical cancer. Based on in vitro data, the combination of trastuzumab and docetaxel may be one of the most synergistic ones of all the trastuzumab combinations available to date. These in vitro findings are supported by the clinical data suggesting high activity of the docetaxel plus trastuzumab regimen in the adjuvant, preoperative systemic, and metastatic setting. Long duration of adjuvant administration of single-agent trastuzumab might also result in cancer cell eradication and gradual death of dormant cancer cell populations, although the bulk of evidence suggests that trastuzumab administered in combination with chemotherapy is more effective that trastuzumab given as a single agent. (Joensuu – SOLD protocol)

[21] Sledge GW, O'Niell A, Thor AD, Kahanic SP, Zander SP, Davidson NE. Adjuvant trastuzuman: long term results of E2198. Poster presentation 2075, SABCS 2006 http://www.abstracts2view.com/sabcs06/view.php?nu=SABCS06L_561

[22] E2198 was a small randomized adjuvant trial that examined the cardiac effects of HP (trastuzumab [H] plus 3 weekly administered paclitaxel [P]) followed by AC (doxorubicin [A] plus cyclophosphamide [C]) among 234 breast cancer patients with HER2-positive (IHC 2+ or 3+) stage II disease.14 The patients were randomly allocated to receive either HP175 q3w X 4 followed by AC q3w x 4 (Arm A; HPx3□ACx4), or to the same regimen followed by H for 52 weeks (Arm B; HPx3□ACx4□H for 52 wks). The median follow-up time at reporting was 64 months. Disease-free survival at 5 years was equivalent for Arms A and B (76% vs. 73%, respectively, P= 0.55), and there was no difference in overall survival between the study arms (5-year survival was 88% for Arm A and 83% for Arm B, P=0.29). Seven study participants were diagnosed with congestive heart failure (Arm A, n=3; Arm B, n=4), all within 3 years from randomization.

PTAC considered, inter alia, that the results of E2198 supported the efficacy of short duration concurrent trastuzumab therapy when administered before anthracycline containing chemotherapy, as demonstrated in the FinHer study.