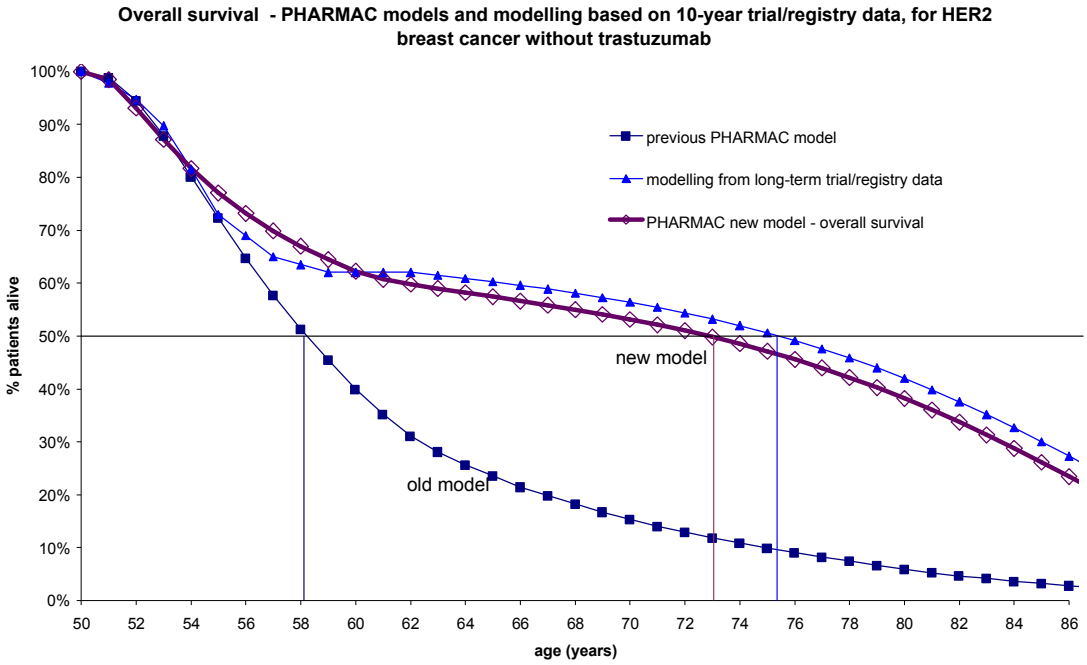
APPENDIX EIGHT

DETAIL OF UPDATES TO CLINICAL INPUTS FOR COST UTILITY ANALYSIS

Revised and updated clinical issues relevant to further cost utility analysis (CUA) for 12 months adjuvant trastuzumab (sequential and concurrent regimens) are as follows:

1. Disease progression of untreated HER-2 positive disease (baseline disease free survival and overall survival curves)

The CUA model has been amended to better reflect the base epidemiology of HER2 positive breast cancer. 10-year follow-up registry and adjuvant chemotherapy trial data indicate improved prognosis in patients with HER-2 positive disease not treated with trastuzumab (i.e. baseline standard care) than assumed in previous PHARMAC CUAs. Modelling integrates the new 10-year patterns with overall 2-3 year median survival data from the clinical trials to derive new baseline overall survival curves.



Modelling has then back-calculated disease free survival (DFS) and consequent risks for disease progression for standard care, and then applied/overlaid trial-based relative risks to derive DFS for trastuzumab-treated patients with consequent disease risks and overall survival.

Further information is in Annex One (Disease progression) to this appendix.

2. Comparative efficacy of the 9 weeks concurrent, 12 months sequential and 12 months concurrent regimens in terms of disease free survival and overall survival:

The clinical study-derived specific relative risks for disease progression affecting the CUA model have been updated to reflect new trial data reported since last analysis.

The central estimates of effect for disease progression of the differing regimens are derived from the reported hazard ratios (HRs), with the following component data included and this pooled information used to derive overall HRs for treatment regimens (using fixed effects models):

- HERA 23-month median follow-up, N9831 sequential arm and PACS04 trials for 12-months sequential treatment;
- Combined B31 trial and N9831 concurrent arm 2.9 year median follow-up and BCIRG006 AC-TH arm 3-year median follow-up for 12-months concurrent treatment; and
- FinHer 3-year median follow-up results for 9 weeks concurrent treatment.

Sensitivity analyses model 'worst case' probabilities for disease progression, derived from the upper 95% confidences limits for the HRs as reported, to mitigate differential biases from the greater imprecision (wider confidence limits) with the 9 week concurrent regimen.

Note that the FinHer central estimates for disease progression events are better than those of overall 12 month concurrent treatment. However, similar to the previous CUAs, modelling in the base case sensitivity analysis conservatively assumes no difference in reported efficacy between the two regimens, and hence applies the rates for 12 months concurrent treatment to nine-week treatment (rather than using FinHer's central estimates).

The previous and updated relative risks for disease free survival (DFS) are therefore as follows

	Base case disease event % RRR* (HR, RR)	**'worst case' disease event %RRR (HR, RR)**
Previous Models:		
12 months sequential	46% (0.54)	(not done)
9 weeks concurrent	46% (0.54)	17% (0.83)
Updated:		
12 months sequential	28% (0.72, 0.75)	22% (0.78, 0.85)
12 months concurrent	47% (0.53, 0.60)	40% (0.60, 0.67)
9 weeks concurrent	47% (0.53, 0.60)	17% (0.83, 0.84)

*where "RRR" is based on hazard ratios (1-HR), not relative risks

The benefit of trastuzumab treatment is modelled by applying the relative risks baseline disease progression rate in the trastuzumab treatment arms. This method gives three year absolute risk reductions that are greater than reported for the 12 month concurrent regimens; this favours the 12 month concurrent trastuzumab regimen.

Further information on how these relative risks were derived is contained in Annex Two (Relative risks/event probabilities used in cost utility analysis) to this appendix.

3. Durability of response to trastuzumab, including a waning of treatment effect:

The durability of the effectiveness of trastuzumab has been amended in the updated CUA, for both the time that evidence extends to (within clinical trials) and extrapolation of this benefit to the long-

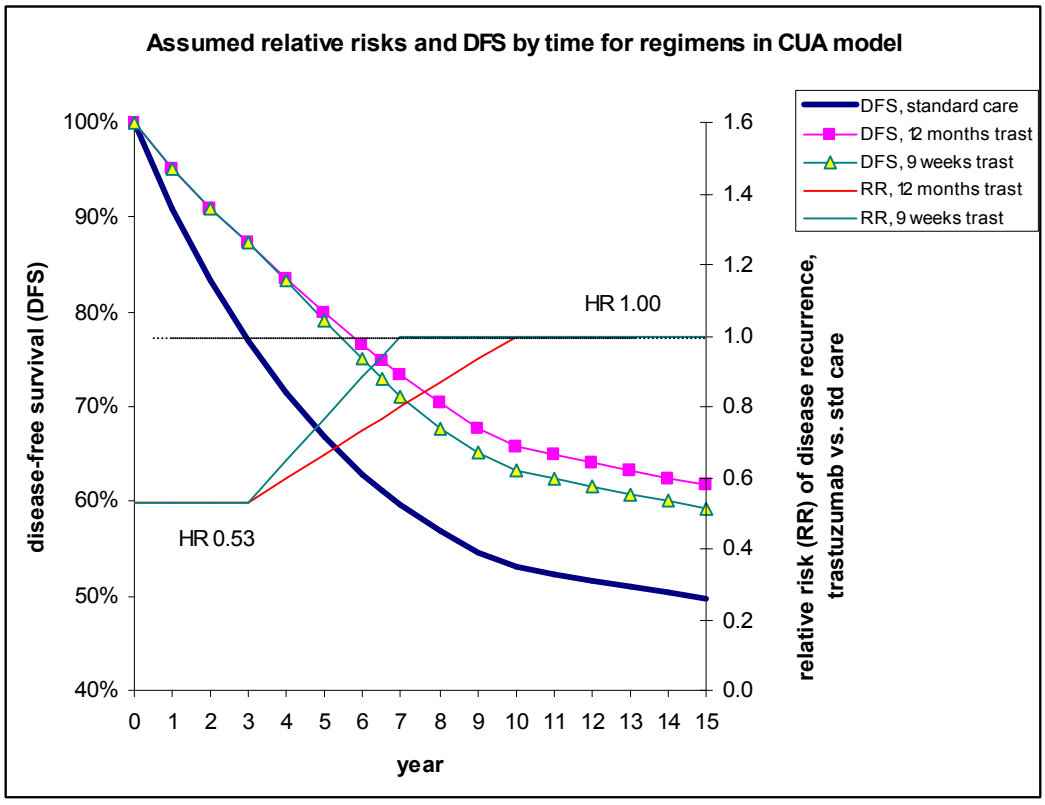
term. This accounts for emerging evidence of both changes in treatment effects over time reported to date within most of the trials, and increasing uncertainty regarding treatment effects long-term.

Some long-term waning of treatment benefit is included in the base case sensitivity analysis of the updated CUA model, and assumptions of either no waning of effect or different rates of waning are modelled in further sensitivity analyses.

PHARMAC's updated modelling for durability of response now assumes a three-year period of benefit from adjuvant trastuzumab for all regimens, being the median follow-up extent to which there is reliable published evidence from the clinical trial data reported to date.

For extrapolation of the data to model the long-term effect of treatment, base case modelling assumes a medium-term benefit scenario, where some benefit remains in the medium term up to 10 years (given the above indications of disease remission/quiescence after 10 years). This assumes a proportion of patients treated with trastuzumab will have a lower risk of disease recurrence that continues beyond the period of benefit, but that the risks of disease progression in trastuzumab-treated patients move towards that of untreated patients over time, by 10 years adopting the baseline risk for disease recurrence, with no further treatment benefit. The extent of waning in the intervening years (4 to 9) depends on the regimen, and is varied for the sensitivity analyses. For 12 months concurrent and sequential regimens, modelling assumes relative risks reach 1.0 at year 10 (i.e. 7 years after the end of the period-of-full-benefit). For the nine weeks concurrent regimen, modelling assumes relative risks deteriorate faster to reach 1.0 at year 6-7 (i.e. 3.5 years after the end of the period-of-full-benefit).

Relative risks for disease events and consequent DFS are therefore modelled over time for treatment regimens as follows:



For short-term benefit, base case modelling assumes the above three-year period of benefit for all regimens, and conservatively assumes no intra-trial waning of effect, using constant risk reductions over the initial three years of the model.

Further information on durability of effect is contained in Annex Three (Durability of trastuzumab effect: modelling waning of treatment effect) to this appendix.

4. Cardiotoxicity of trastuzumab:

The model assumes the following cumulative incremental rates of symptomatic heart failure and severe cardiac events (rates are incremental those reported for standard care:

Treatment regimen	Symptomatic congestive heart failure	Severe cardiac adverse effects
12 months sequential post AC	1.13%	0.54%
12 months concurrent post AC	6%	3%
9 weeks concurrent pre-AC	1.13%	0.54%

Cardiac events reported in the FinHer trial may have been comparatively low because of possible artefact (underpowered to detect and measure cardiac toxicity; lessened sensitivity (LVEF detection); lower than standard doses of epirubicin), rather than nine-week concurrent regimen being truly less cardiotoxic than long duration regimens. Pending further data, the updated model therefore now assumes the rates of adverse cardiac effects for the nine weeks concurrent regimen to be the same as those reported for the 12 months sequential regimen. This assumption is conservative, disfavouring the nine week concurrent trastuzumab regimen.

Asymptomatic decreases in LVEF have not been modelled for this updated analysis because these are not classified as severe, would potentially not be identified in clinical practice due to the asymptomatic nature, and appear to be reversible on cessation of treatment. If the prevalence of asymptomatic decreases in LVEF, and a treatment protocol for the management of this condition, were to be included in the analysis this would disfavour the concurrent 12 months regimen.

Sensitivity analyses modelled increased rates of cardiotoxicity, to reflect the likelihood that some patients treated in clinical practice in New Zealand would have poorer baseline heart function and pose higher risks for cardiotoxicity (not having met the strict inclusion criteria for the clinical trials). This assumption disfavours trastuzumab, especially the 12 months concurrent regimen, hence modelled in the sensitivity analysis rather than the base case.

The CUA model does not adjust for different patient numbers receiving trastuzumab treatment with the different regimens. Conceivably, more patients may be able to receive treatment with the nine week concurrent regimen than the longer duration regimens, due to possible lower cardiotoxicity from it being given before anthracycline treatment as per the FinHer protocol. This is a conservative assumption (favours 12 months treatment).

For further information on trastuzumab-associated cardiotoxicity, including the key references for this information, see Annex Four (Cardiotoxicity with trastuzumab) to this appendix.

Annexes to Appendix 8:

Annex One: Baseline disease progression

Annex Two: Relative risks/event probabilities used in cost utility analysis

Annex Three: Durability of trastuzumab effect: modelling waning of treatment effect

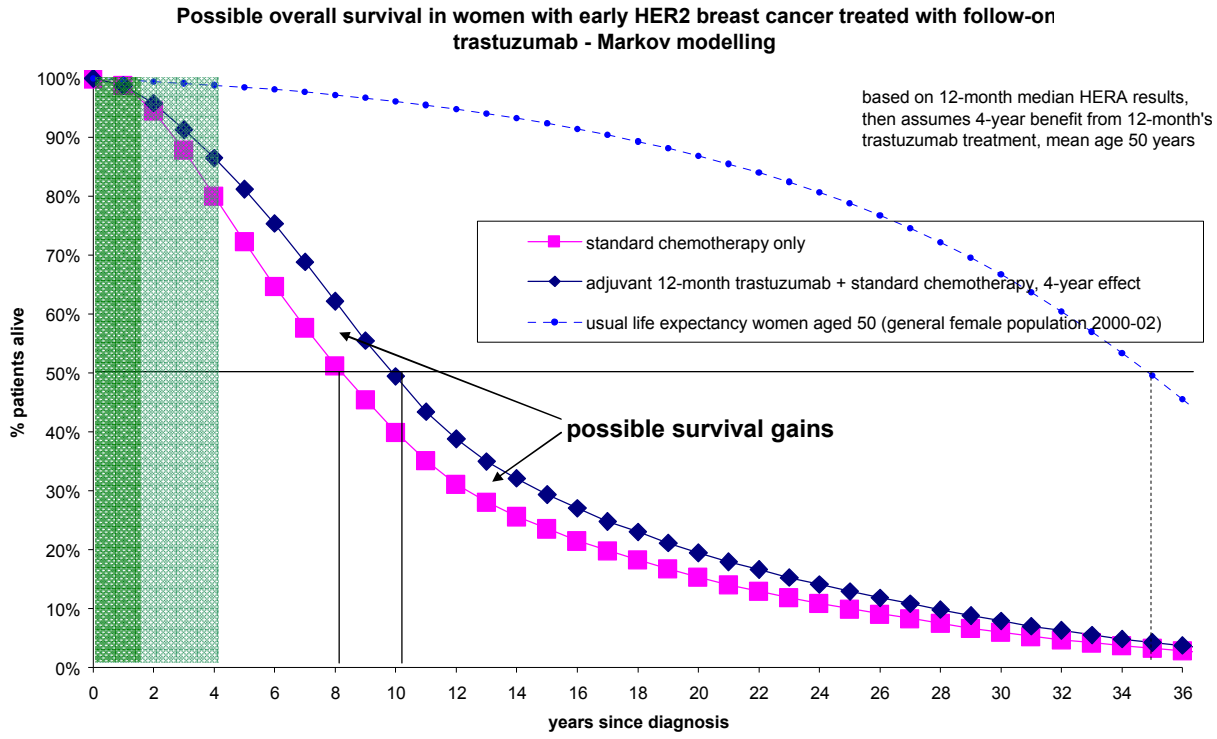
Annex Four: Cardiotoxicity with trastuzumab

Annex One

Baseline disease progression

The updated CUA model has been amended to better reflect the base epidemiology of HER2 +ve breast cancer, where survival analyses seem to suggest initially highly aggressive disease with early excess mortality but then quiescence after 5 years or so.

Previous cost utility modelling (TAR 75 August 2006, TAR 75b April 2007) assumed constant annual risks of disease progression, causing a persistent decline in survival with time, as seen in the following graph.

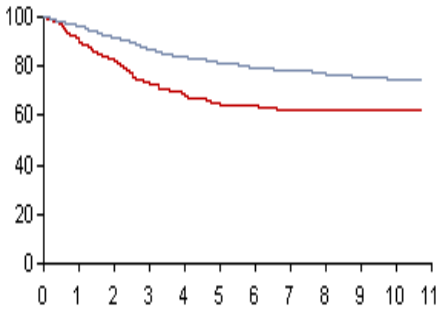


However, as discussed in the TAR, recently published 10-year follow-up data from a large clinical trial[1], along with available 10-year follow-up registry data from Finland[2], show survival patterns for HER2-positive breast cancer treated with current standard care, whereby survival stabilises after 5-6 years (curves 'flatten out') – similar to all breast cancers.

[1] Pritchard KI, Shepherd LE, O'Malley FP, Andrulis IL, Tu D, Bramwell VH, Levine MN; National Cancer Institute of Canada Clinical Trials Group. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med. 2006 May 18;354(20):2103-11. http://content.nejm.org/cgi/content/full/354/20/2103. from Figure 1. Relapse-free Survival (Panel A) and Overall Survival (Panel B) among Women with Breast Cancer, According to HER2 Amplification Status on FISH.
[2] FinProg data (http://www.finprog.org/) – HER2-positive vs. HER-2 negative

http://www.finprog.org/

	Years	1	3	5	8	10
her2+	Cum. Survival	90%	73%	65%	62%	62%
her2-	Cum. Survival:	96%	87%	82%	77%	75%



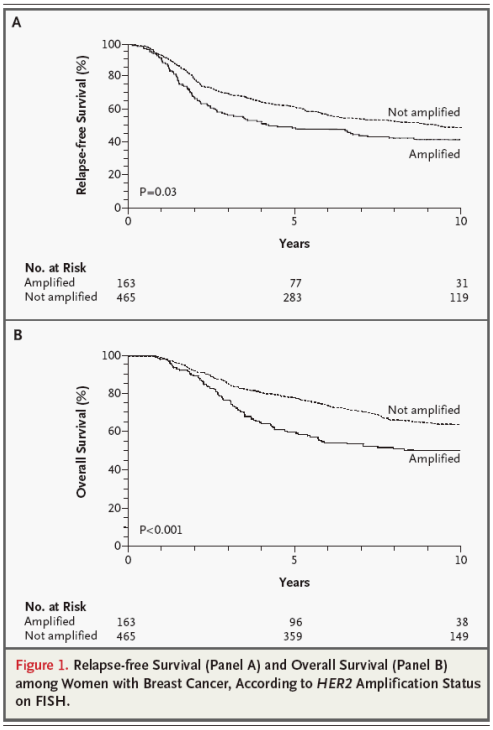
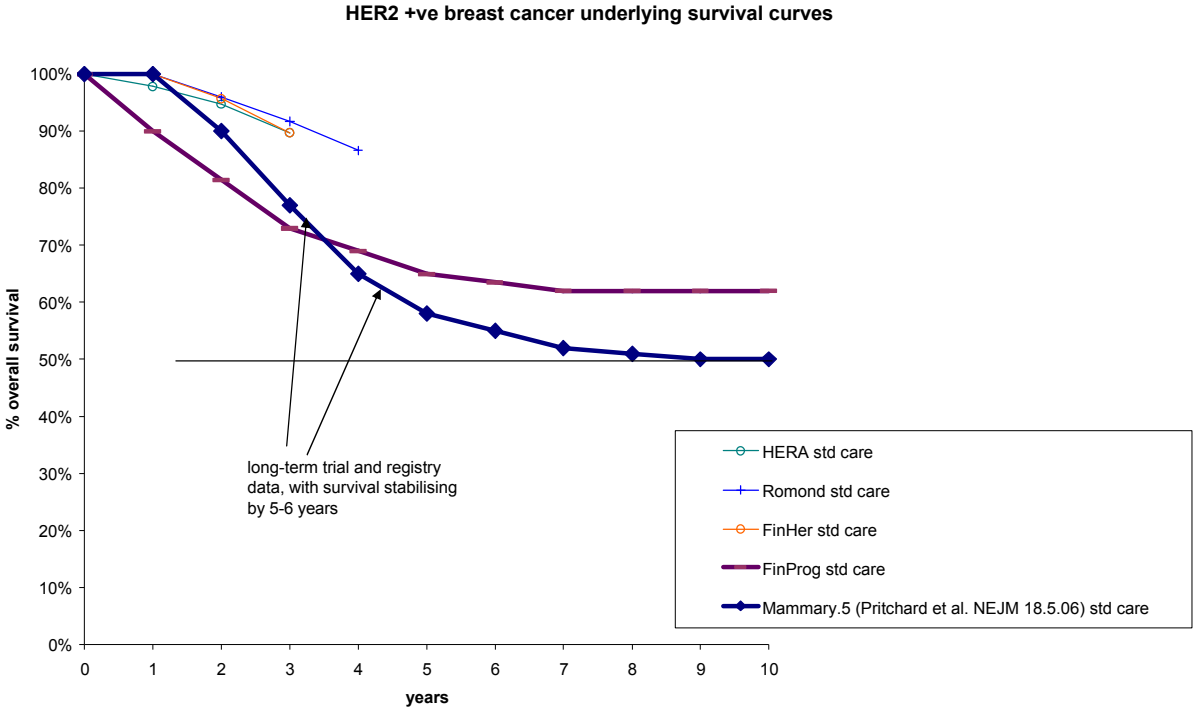


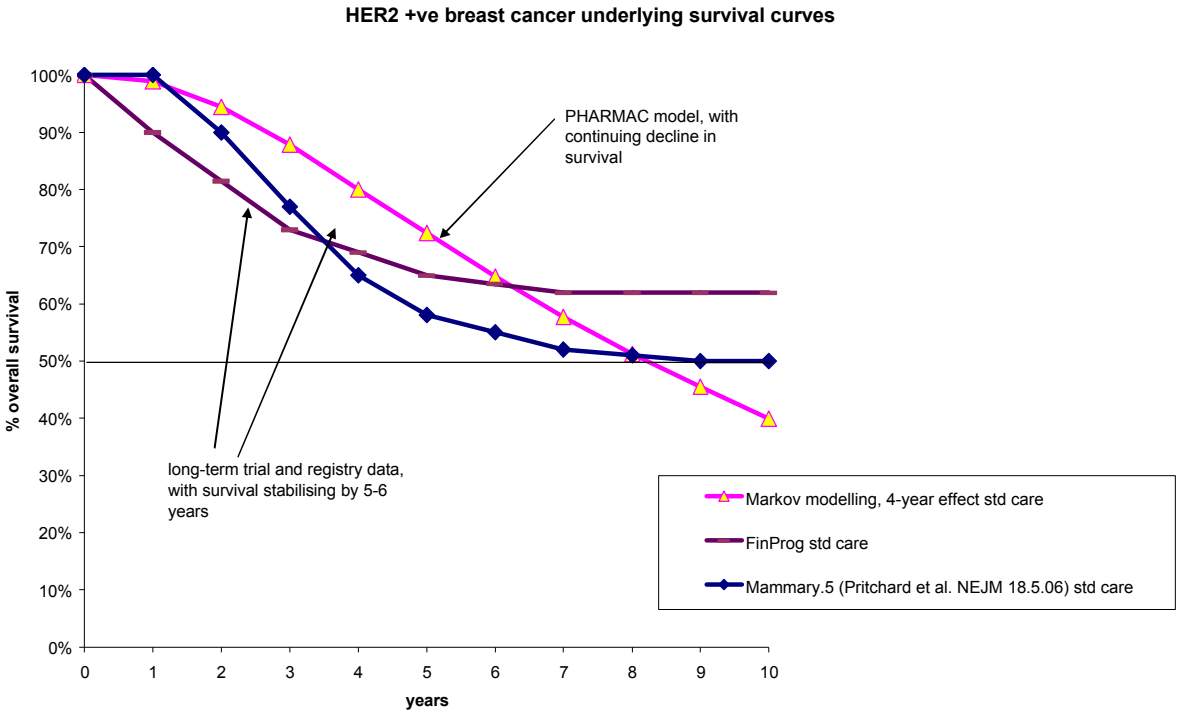
Figure 1. Relapse-free Survival (Panel A) and Overall Survival (Panel B) among Women with Breast Cancer, According to *HER2* Amplification Status on FISH.

These data compared suggest with the epidemiological data

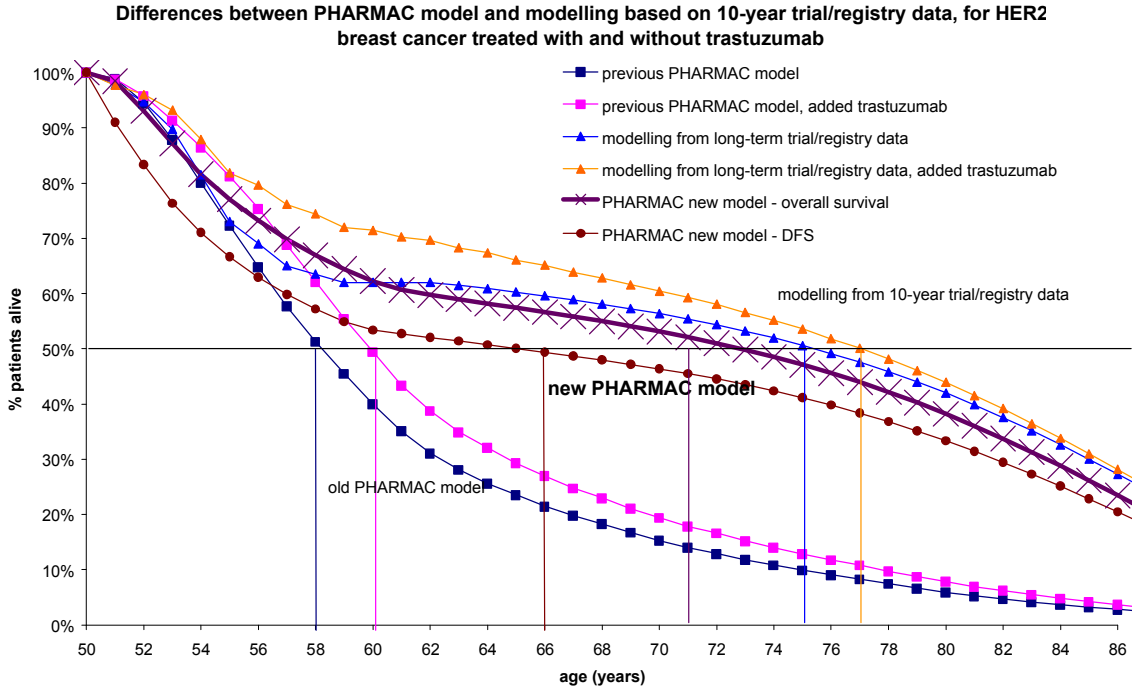


These patterns are distinct from the continuing decline in survival seen in Markov modelling (in the PHARMAC model, analysis undertaken by ScHARR for NICE[3], and models developed by Roche and submitted to NICE) from ongoing and cumulating culminating mortality due to a persisting (if eventually reduced) risk of breast cancer recurrence.

[3] Ward S, Pilgrim H, Hind D. Trastuzumab for the Treatment of Primary Breast Cancer in HER2 Positive Women: A Single Technology Appraisal. University of Sheffield School of Health and Related Research (ScHARR), May 2006. http://www.nice.org.uk/page.aspx?o=328487. Update with revised cost per QALY at http://www.nice.org.uk/page.aspx?o=328530

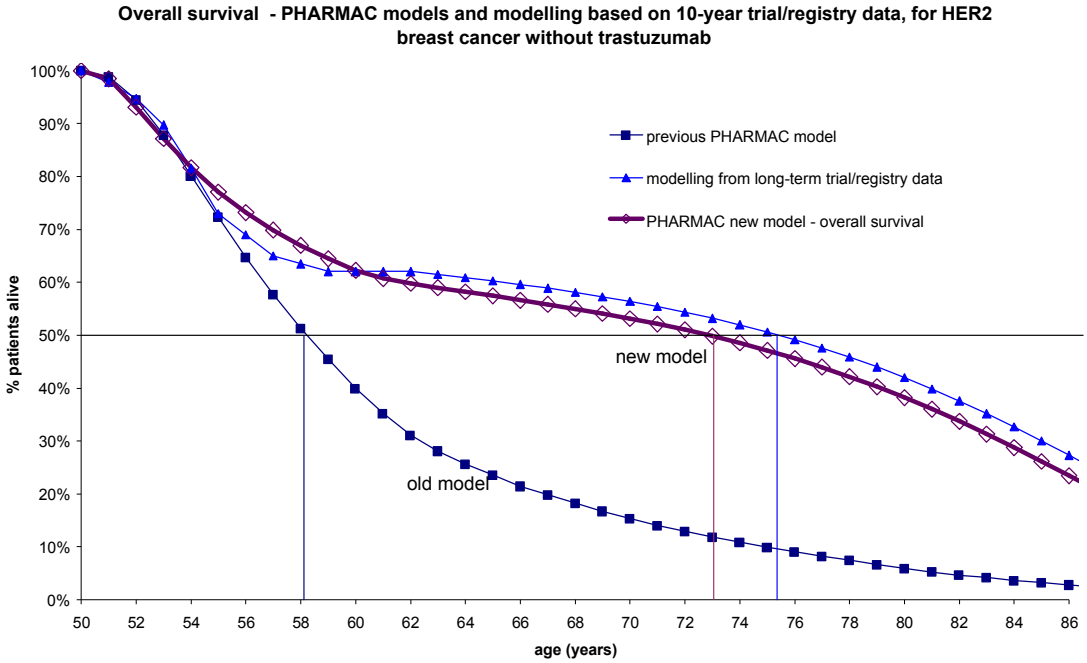


The graph below shows the effects on survival of disparity between PHARMAC's previous Markov modelling and the long-term trial and registry data, extrapolating beyond 10 years and modelling the effects of disease event reductions from trastuzumab.

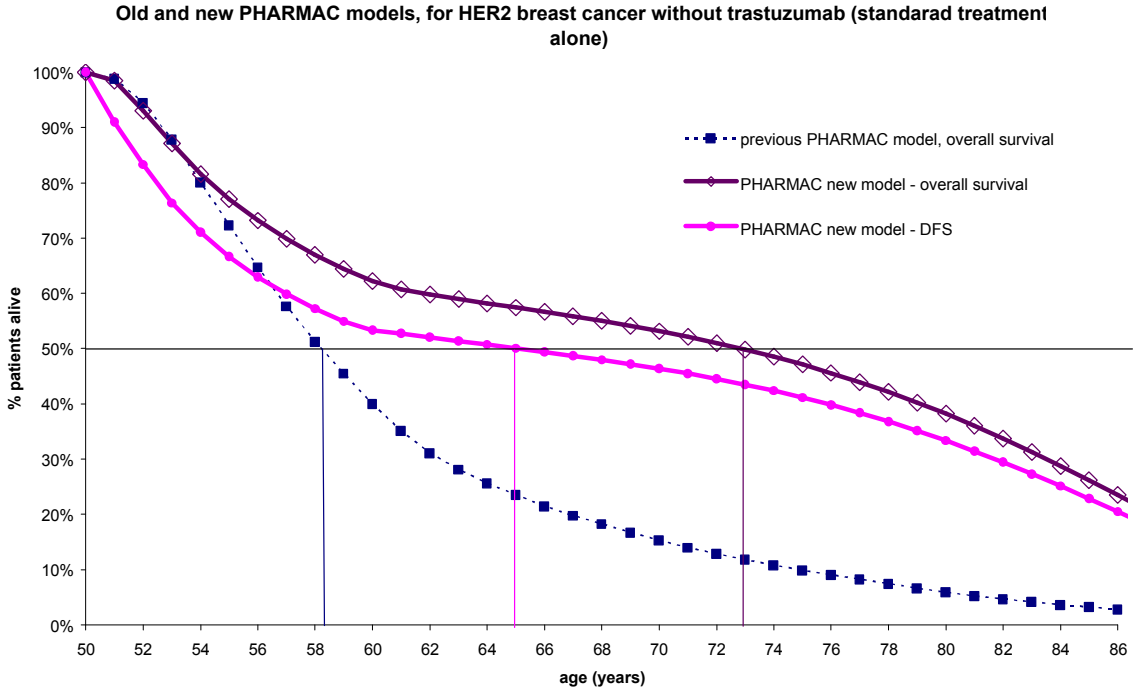


In terms of disease modelling, the above 10-year overall survival registry and adjuvant chemotherapy trial data suggest that if patients are remission free for 10 years, then their risk of death is not significantly different from patients who have never had node positive early breast cancer (as with remission for cancers in general).

Therefore, updated modelling now uses baseline disease event rates that will reasonably reproduce the above flattened overall survival curves for untreated patients, onto which is applied/overlaid relative risk reductions to derive DFS and OS patterns for treated patients (see below). In effect, the OS survival curves level out after patients are remission free for 10 years. Modelling now integrates the above registry and trial 10-year patterns with overall 2-3 year median survival data from the clinical trials to derive overall survival for standard care patients (see figure below):

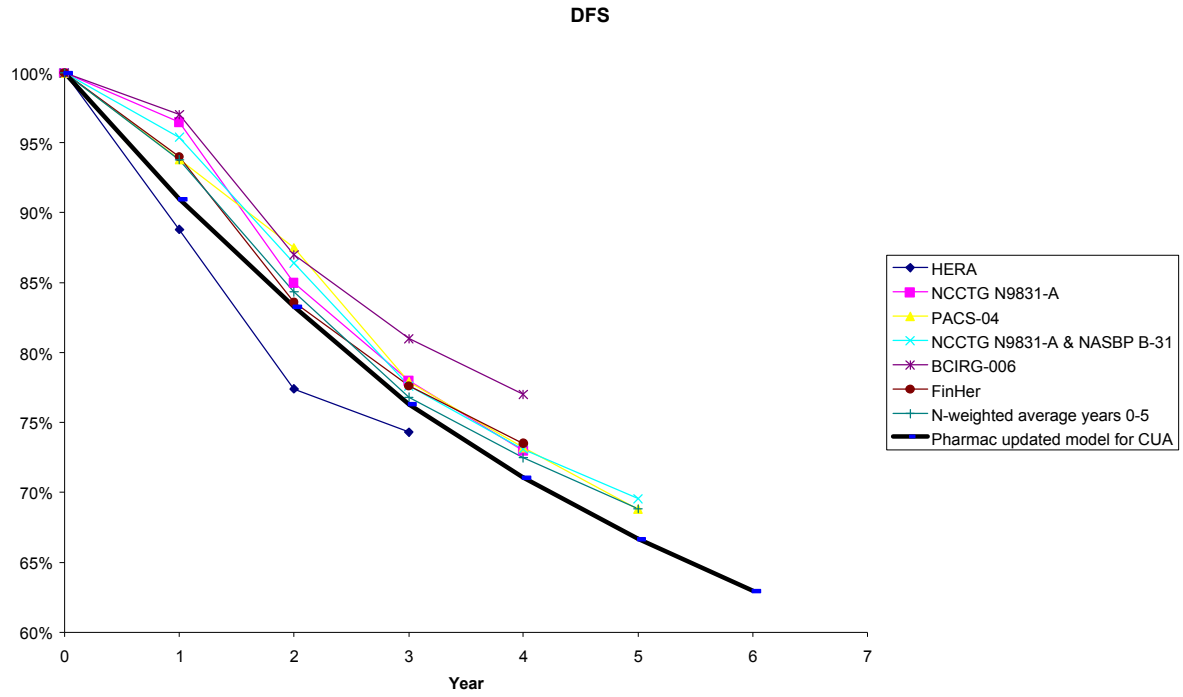


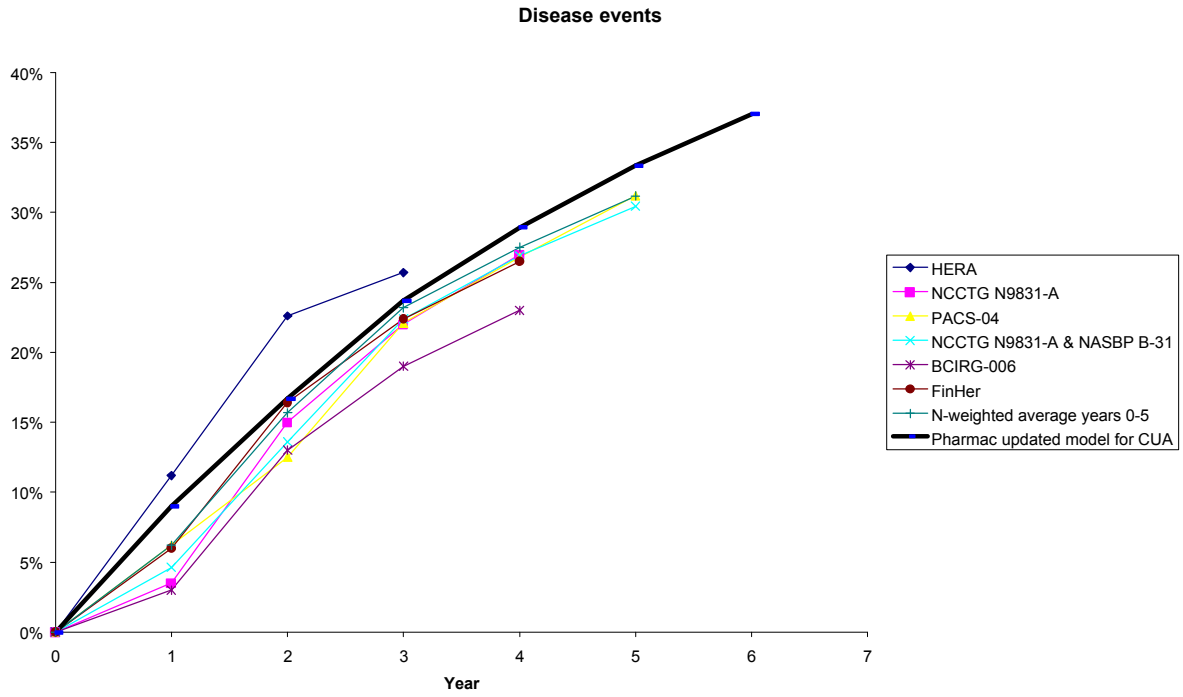
Modelling then uses the new overall survival curve to back-calculate DFS and consequent risks for disease progression for standard care (see figure below):

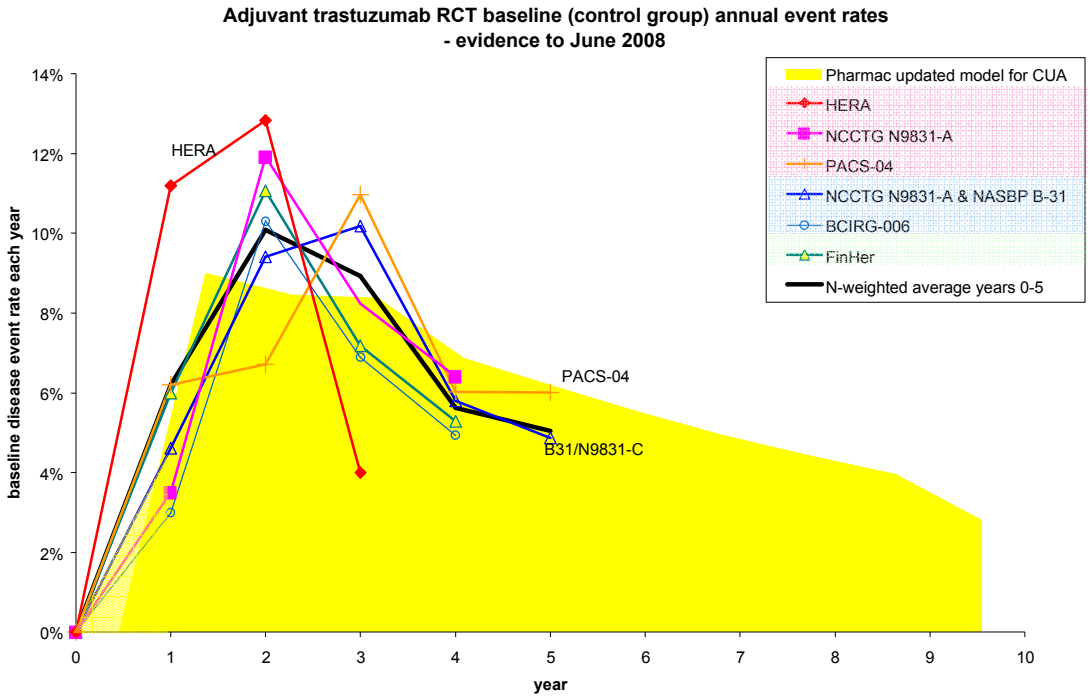


Modelling then applies/overlays trial-based relative risks to derive DFS for trastuzumab-treated patients with consequent disease risks and overall survival.

The effect of any such changes to the model can be seen by back-calculating disease events and comparing these with data from the relevant adjuvant trastuzumab trials. This indicates a close fit between the new model and the standard care populations in the trials, as can be seen in the following graphs:







As noted above, 10-year overall survival patterns in the FinProg registry suggest that women who are disease-free for 10 years have age-specific risks of death not appreciably different from women in the general population, as is assumed for remission in many cancers generally.

The effect of this on cost utility modelling is for this to logically assume that after 10 years that remission has occurred – that is, if disease recurrence had not occurred already, then women's risks of disease in the model is no more than women without breast cancer. Cost utility scenarios in effect need only a 10 year time horizon for efficacy, beyond which both trastuzumab-treated and untreated HER2-positive early breast cancer patients are assumed to have the same age-specific risks of disease events as patients without HER2-positive early breast cancer, meaning age-specific relative risks of 1.0 for trastuzumab and standard care relative to women in general beyond 10 years.

Annex Two

Relative risks/event probabilities used in cost utility analysis

Adjuvant trastuzumab for early breast cancer associated with anthracyclines/taxanes can be given in two main sequences: sequentially after concurrently with or other chemotherapy. Regimen durations vary between 8-9 weeks (pre-anthracycline concurrent, as per the FinHer trial), 6 months (PHARE, PERSEPHONE), 12 months (post-anthracycline concurrent: NSABP-B31, NCCTG-N9831 arm C, BCIRG006 arm AC-TH; sequential post-anthracycline: HERA, N9831 arm B, PACS04), or 24 months (sequential post-anthracycline: HERA).

Previous cost utility modelling (TAR 75 August 2006, TAR 75b April 2007) used transitional probabilities for disease event rates for the licensed 12 month sequential trastuzumab treatment. These probabilities were derived from the 12 month median follow-up results of the HERA trial (which have subsequently been outdated by the 24 month follow up data that show a decrease in treatment effect).

Previous modelling applied the 12 month follow-up probabilities for four years (being expected known durability of effect). Modelling for base case analyses conservatively applied exactly the same rates to derive probabilities for nine-week treatment (rather than using FinHer's lower central HRs, which would imply better efficacy), applied again over four years.

Since then, the current proposal to decline funding of 12 months trastuzumab treatment and the emergence of new evidence (including wider appreciation of the impact of poorly-disseminated data demonstrating sequential treatment does not always produce the significant results seen in the HERA trial), means that applying the 12 month HERA follow-up data to all scenarios (regardless of sequence) may be no longer accurate or valid.

Hence, updated modelling now uses the following trial-derived updated specific relative risks to scenarios of disease progression and length of treatment effect. Base case analyses use central estimates of effect for disease progression events (being from the reported hazard ratios (HRs)). , 'Worst case' probabilities are used sensitivity analyses, being from the upper 95% CIs for the HRs as reported. Component data comprise:

- 12-months sequential will use pooled results from the HERA 23-month median follow-up, N9831 sequential arm and PACS04 trials (fixed effects model).
- 12-months concurrent will use pooled results of the 2.9 year median follow-up of the N9831 concurrent arm and B31 trials (initially combined as 'Romond') and the 3-year median follow-up of the BCIRG006 AC-TH arm (fixed effects model).
- Nine weeks concurrent will us the FinHer 3-year median follow-up results.

Note that FinHer gave central estimates for disease event relative risk reductions, HRs and calculated crude 3-year cumulative relative risks of 58%, 0.42 and 0.45 respectively, being somewhat higher than 12 month concurrent's central rates of 47%, 0.53 and 0.60 respectively. However, similar to the previous CUAs, modelling in base case analyses conservatively assumes no difference in efficacy between the two regimens, and hence applies the rates for 12 months concurrent treatment to for nine-week treatment (rather than using FinHer's better central rates).

Relative risk reductions for disease events will therefore be as follows:

	Base case disease event % RRR* (HR, RR)	'worst case' disease event %RRR (HR, RR)
Was:		
12 months sequential	46% (0.54)	(not done)
9 weeks concurrent	46% (0.54)	17% (0.83)
Proposed:		

12 months sequential	28% (0.72, 0.75)	22% (0.78, 0.85)
12 months concurrent	47% (0.53, 0.60)	40% (0.60, 0.67)
9 weeks concurrent	47% (0.53, 0.60)	17% (0.83, 0.84)

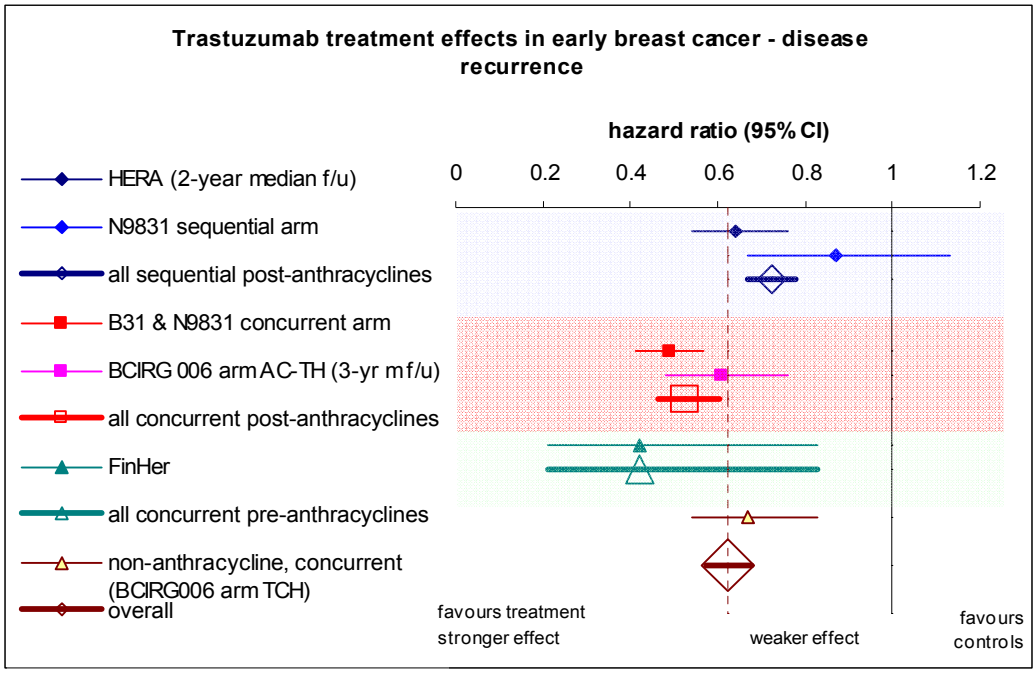
*where "RRR" is based on hazard ratios (1-HR), not relative risks

To meet modelling requirement, relative risks are used rather than hazard ratios. Relative risks therefore used for base case analyses are 0.75 for 12 months sequential and 0.53 for 12 months concurrent and 9 weeks concurrent regimens. For comparative 'worst case' sensitivity analyses, relative risks are 0.85, 0.67 and 0.84 for 12 months sequential, 12 months concurrent and 9 weeks concurrent regimens respectively (from the calculated upper 95% confidence limits for the overall relative risks).

Note that PHARMAC analysis has indicated the following HRs and cumulative RRs with 95% CIs for the above individual trials, and then pooled results, as follows:

Disease free survival

	median f/u (years)	events/pts tmt	cntrl	ARR	hazard ratio HR	-95% CL	+95% CL	relative risk RR	-95% CL	+95% CL
sequential post-anthracyclines										
(previous HERA)	1.0	127/1694	220/1693	5.5%	**0.54**	0.43	0.67	**0.58**	0.47	0.71
(previous overall)	*1.8*	*321/2688*	*438/2677*	*5.9%*	***0.70***	*0.61*	*0.81*	***0.73***	*0.64*	*0.83*
PACS-04	1.5				**0.57**	0.30	1.09			
HERA	1.9	218/1703	321/1698	6.1%	**0.64**	0.54	0.76	**0.68**	0.58	0.79
N9831 sequential arm	1.5	103/985	117/979	1.5%	**0.87**	0.67	1.13	**0.87**	0.68	1.12
PACS-04	4.0	59/260	70/268	3.4%	**0.86**	0.61	1.22	**0.87**	0.64	1.17
overall (variance-weighted HRs, crude RRs)	*2.0*	*380/2948*	*508/2945*	*4.2%*	***0.72***	*0.67*	*0.78*	***0.75***	*0.66*	*0.85*
concurrent post-anthracyclines										
(previous B31 & N9831 arm C)	2.0	134/1672	261/1679	7.5%	**0.48**	0.39	0.59	**0.52**	0.42	0.63
(previous BCIRG 006 arm AC-TH)	1.9	77/1074	147/1073	6.5%	**0.49**	0.37	0.65	**0.52**	0.40	0.68
(previous overall)	*2.4*	*262/2746*	*453/2752*	*8.2%*	***0.53***	*0.46*	*0.62*	***0.58***	*0.50*	*0.67*
B31 & N9831 arm C (2.9 yr median f/u)	2.9	222/1979	397/1989	8.7%	**0.49**	0.41	0.57	**0.56**	0.48	0.65
BCIRG 006 arm AC-TH	3.0	128/1074	192/1073	6.0%	**0.61**	0.48	0.76	**0.67**	0.54	0.82
overall (variance-weighted HRs, crude RRs)	*2.9*	*350/3053*	*589/3062*	*7.7%*	***0.53***	*0.46*	*0.60*	***0.60***	*0.53*	*0.67*
concurrent pre-anthracyclines										
(previous FinHer 3-year interim)	3.0	12/115	27/116	12.8%	**0.42**	0.21	0.83	**0.45**	0.24	0.84
FinHer	3.0	12/115	27/116	12.8%	**0.42**	0.21	0.83	**0.45**	0.24	0.84

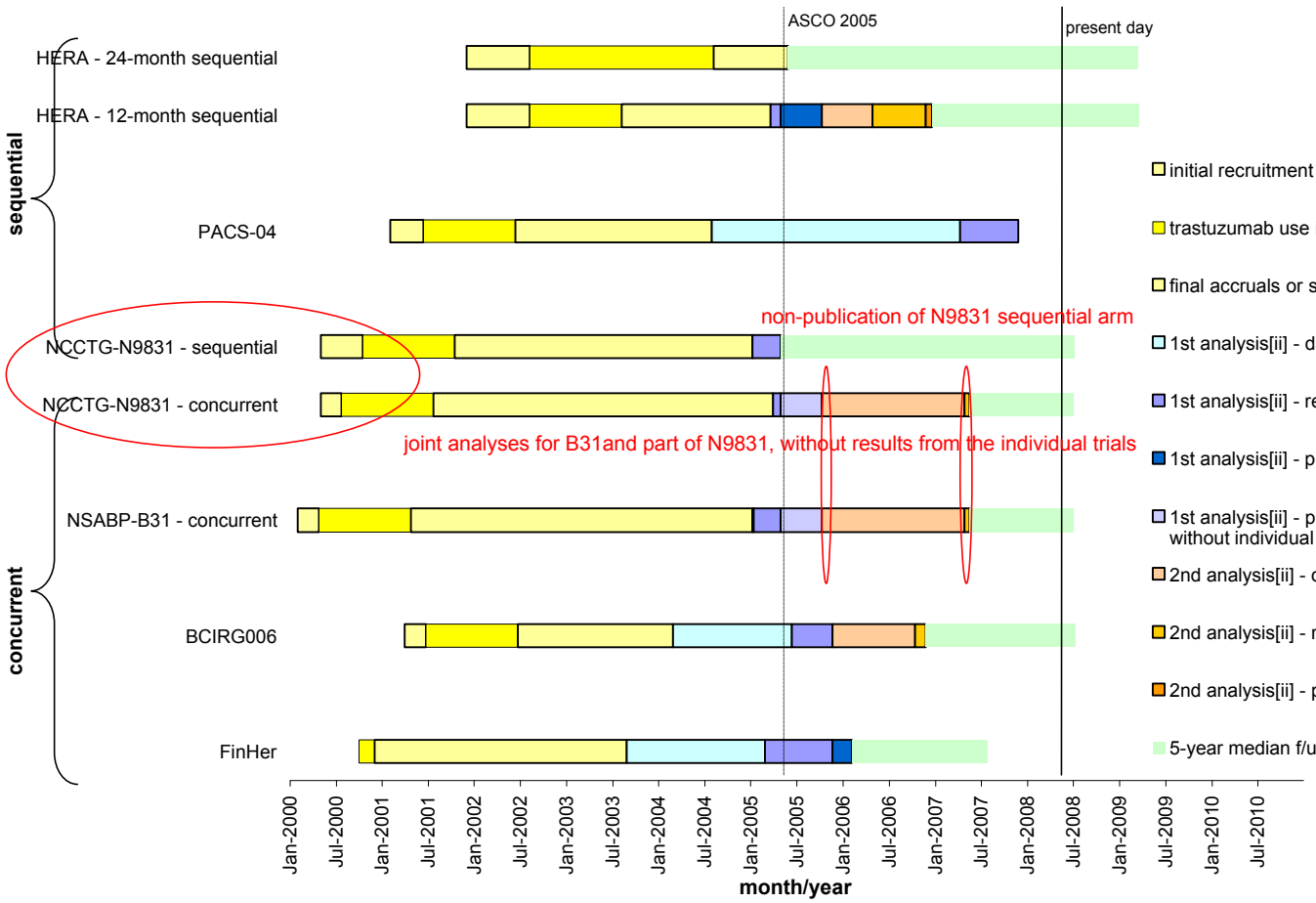


Overall survival

	median f/u (years)	events/pts tmt	cntrl	ARR	hazard ratio HR	-95% CL	+95% CL	relative risk RR	-95% CL	+95% CL
sequential post-anthracyclines										
(previous HERA)	1.0	29/1694	37/1693	0.5%	**0.76**	0.47	1.23	**0.78**	0.48	1.27
(previous overall)										
PACS-04	1.5									
HERA	1.9	59/1703	90/1698	1.8%	**0.66**	0.47	0.91	**0.65**	0.47	0.90
N9831 sequential arm	1.5	36/985	90/1698	0.7%	**0.85**	0.55	1.33	**0.83**	0.54	1.28
PACS-04	4.0	2/260	43/979	-0.4%	**2.06**	0.61	6.99	**2.06**	0.19	22.60
overall	*2.0*	*97/2948*	*1/268*	*1.3%*	***0.76***	*0.65*	*0.88*	***0.72***	*0.56*	*0.94*
concurrent post-anthracyclines										
(previous B31 & N9831 arm C)	2.0	62/1672	92/1679	1.8%	**0.67**	0.48	0.93	**0.68**	0.49	0.93
(previous BCIRG 006 arm AC-TH)	1.9									
(previous overall)										
B31 & N9831 arm C (2.9 yr median f/u)	2.9	)2655/1979	/	2.7%	**0.65**	0.51	0.84	**0.66**	0.52	0.84
BCIRG 006 arm AC-TH	3.0	49/1074	97345/1989	2.9%	**0.59**	0.42	0.85	**0.61**	0.43	0.86
overall	*2.9*	*)2655/3053*	*80/1073*	*2.7%*	***0.63***	*0.51*	*0.77*	***0.64***	*0.53*	*0.78*
concurrent pre-anthracyclines										
FinHer	3.0	12/115	21/116	7.7%	**0.41**	0.16	1.07	**0.58**	0.30	1.12

It is important to highlight that much of the above data remain unpublished (N9831 sequential arm, PACS04, B31/N9831 concurrent arm 2.9-year median follow-up, BCIRG006). The time courses of all relevant trials, including reporting times, can be seen in the following graph:

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



All 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, PACS-04) have reported interim efficacy results, but have varied by the timing of patient accruals, when results were initially reported, and when (if) published.

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 and has not reported outcomes against standard chemotherapy treatment.

Further details are available, as needed, in published work around these factors in the PHARMAC's article in the NZ Medical Journal of June 2007[4], its Appendix Four,[5] and the Lancet article May 2007 about publication bias with N9831's sequential arm.[6]

[4] 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
[5] Appendix 4: Clinical effectiveness (including publication bias) http://www.nzma.org.nz/journal/120-1256/2593/Afour.pdf
[6] Metcalfe S, Burgess C, Laking G, Evans J, Wells S, Crausaz S. Trastuzumab: possible publication bias. Lancet. 2008 May 17;371(9625):1646-8. http://www.thelancet.com/journals/lancet/article/PIIS0140673608607060/fulltext

Annex Three

Durability of trastuzumab effect: modelling waning of treatment effect

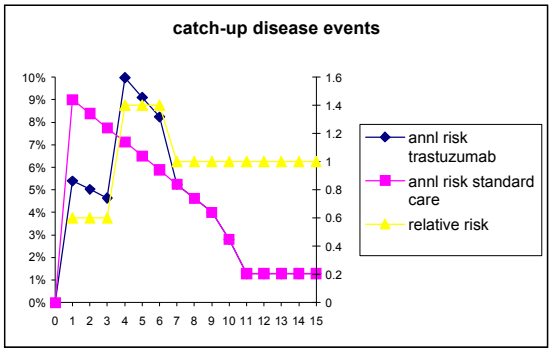
Previous cost utility modelling (TAR 75 August 2006, TAR 75b April 2007) assumed that relative risk reductions for disease events were constant over the duration of benefit, and that in turn that duration of benefit lasted for four years. Emerging information since means these assumptions require amendment.

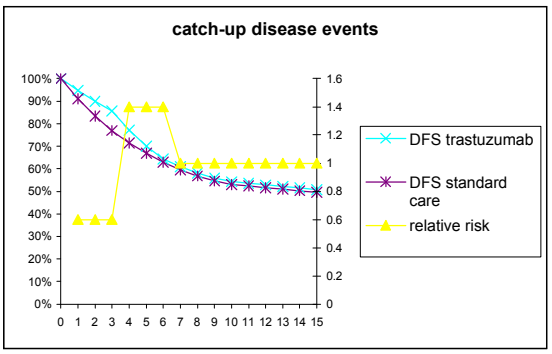
Models of disease progression and treatment benefit typically consider changes in treatment effects (relative risk) over time, both within the time that there is evidence for (in clinical trials) and extrapolating to time beyond. Such modelling is necessary for adjuvant trastuzumab, where there is both evidence of changes in treatment effects between interim analyses for most studies, and uncertainty regarding treatment effects long-term beyond the trial data reported to date.

Options for models include:

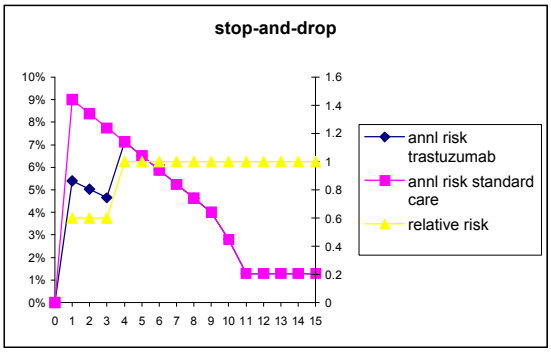
A. Long-term durability of treatment effects (extrapolated waning of effect)

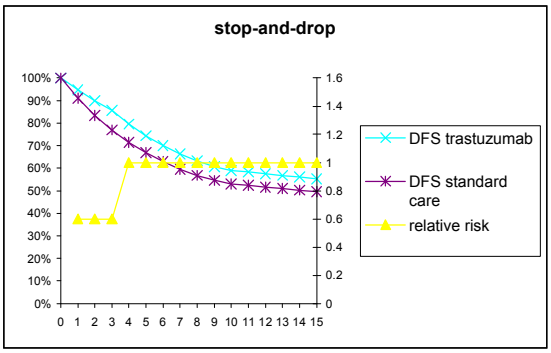
1. **Catch-up disease progression scenario**, where at the end of a defined period of benefit trastuzumab-treated patients adopt the initial baseline risk of disease recurrence, so that DFS curves then converge. This means that for time that trastuzumab-treated patients in effect have a higher annual risk of events than standard care patients, with resultant relative risks greater then 1.0 (see the following graphs of annual and relative risks and disease-free survival for the catch-up scenario):



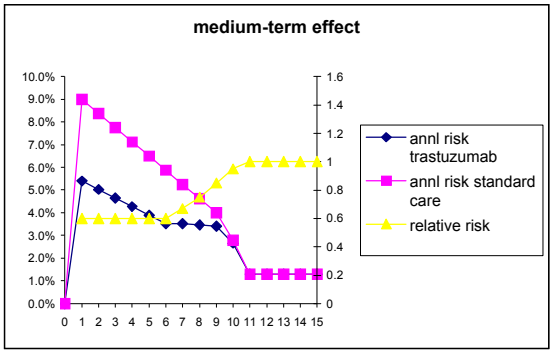


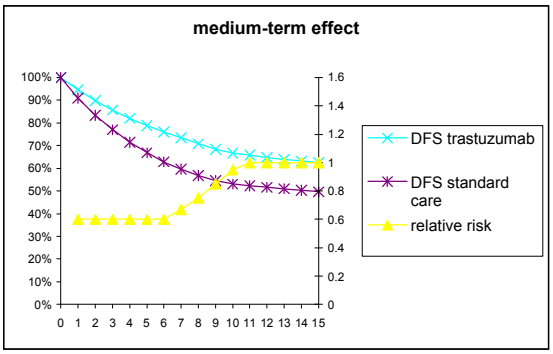
2. **'Stop and drop' scenario**, where patients treated with trastuzumab adopt the standard care arm's cumulative baseline risk of disease recurrence at the end of the defined period of benefit, the relative risk becoming 1.0 at that time, so that DFS curves no longer diverge but run parallel and there is no more treatment benefit (see graphs):



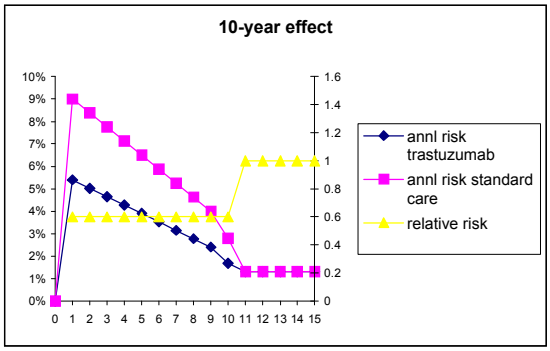


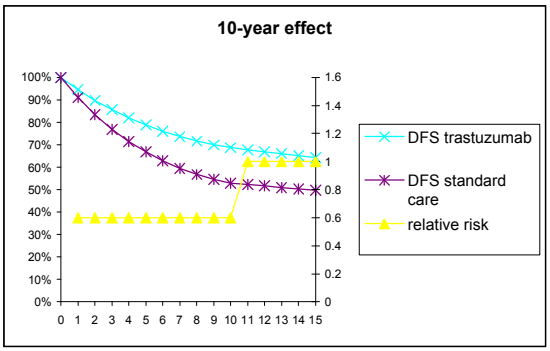
3. **Medium-term benefit scenario**, where the benefit of trastuzumab is not long-lasting but that some benefit would remain in the medium term up to 10 years (given the above indications of disease remission/quiescence after 10 years). This assumes a proportion of patients treated with trastuzumab would have a lower risk of disease recurrence that continues beyond the period of benefit, but that the relative risk of disease progression in trastuzumab-treated patients would move towards 1.0 over time - where reaching a relative risk of 1.0 means the treatment group eventually adopts the baseline risk for disease recurrence, with no further treatment benefit (see graphs):





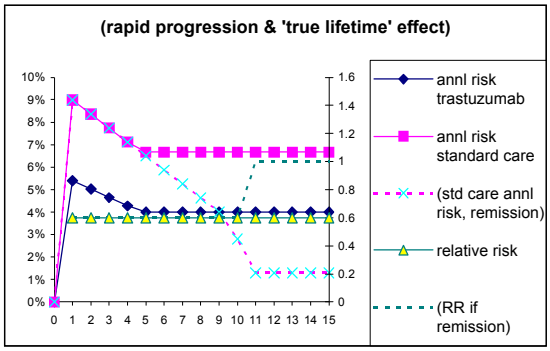
4. **Lifetime benefit scenario**, where the benefits seen in the trials over the first three years are maintained indefinitely for the rest of patients' lives, so that relative risks remain constant and below 1.0 and disease free survival curves continue to diverge for the first 10 years (after which there is remission anyway); see graphs:

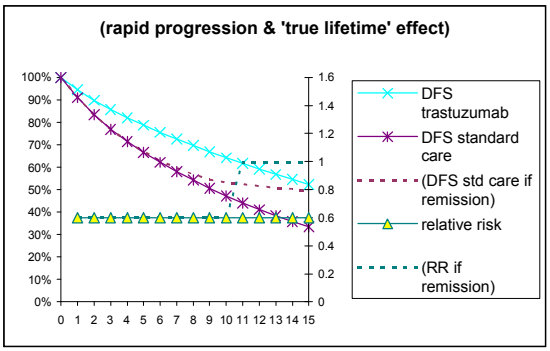




As noted in Annexe One, modelling assumes from epidemiological data a 10-year time horizon for treatment efficacy, after which remission has occurred with age-specific risks of death equate to those of women in the general population, as is assumed for remission in many cancers generally. In other words, modelling assumes that if disease recurrence has not occurred already, then women's risk of disease in the model is no more than women without breast cancer – beyond 10 years, both trastuzumab-treated and untreated HER2-positive early breast cancer patients are assumed to have the same age-specific risks of disease events as patients without HER2-positive early breast cancer, meaning age-specific relative risks of 1.0 for trastuzumab and standard care relative to women in general.

Note that the above constraint of disease remission at 10 years, with age-specific risks for both treated and standard care patients adopting the low background risk of women in general, does not allow for modelling a scenario of continuing DFS divergence beyond 10 year (a 'true lifetime' effect). Such divergence was assumed in the Roche and others' CUAs, and could be modelling alongside rapid disease progression (which occurred in PHARMAC's previous CUA (TAR 75) and the Roche and ScHARR models):





These four options, alongside a combined rapid progression/'true lifetime' effect model, are summarised and their effects can be compared in the following graphs

Figure: Annual risks of disease events in models of long-term durability with trastuzumab vs. standard care

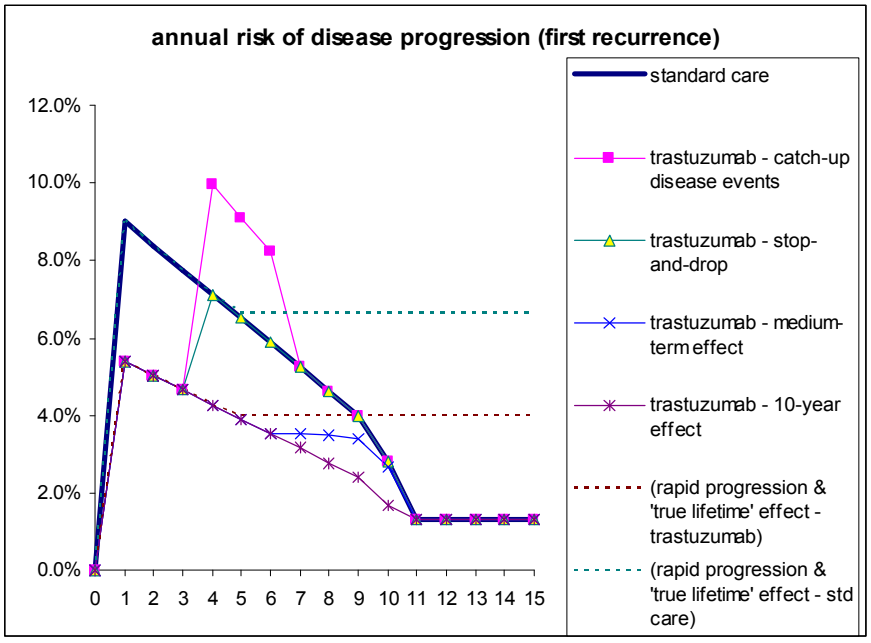


Figure: Relative risks of disease events in models of long-term durability with trastuzumab vs. standard care

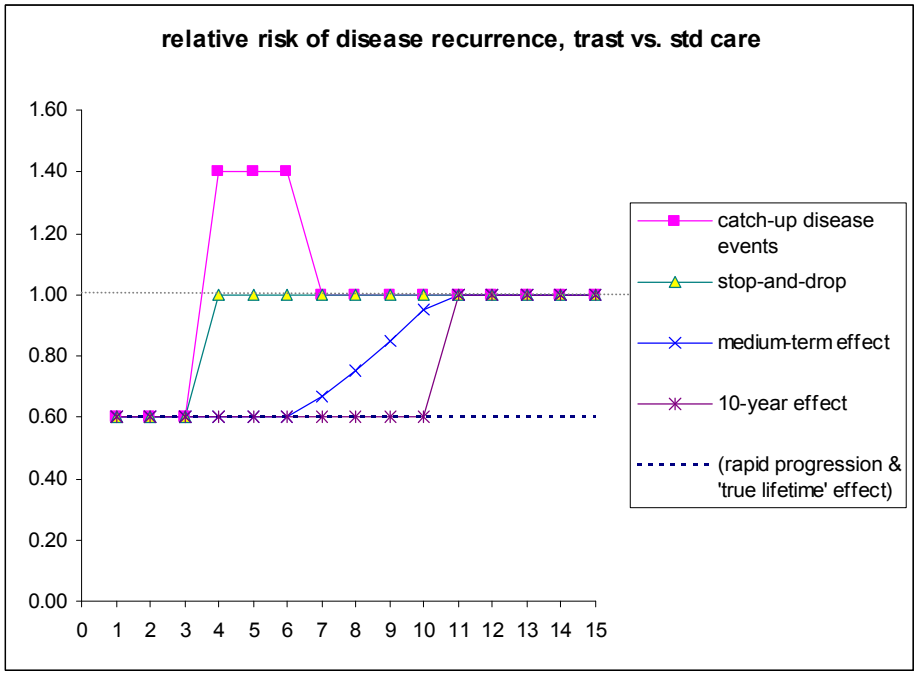
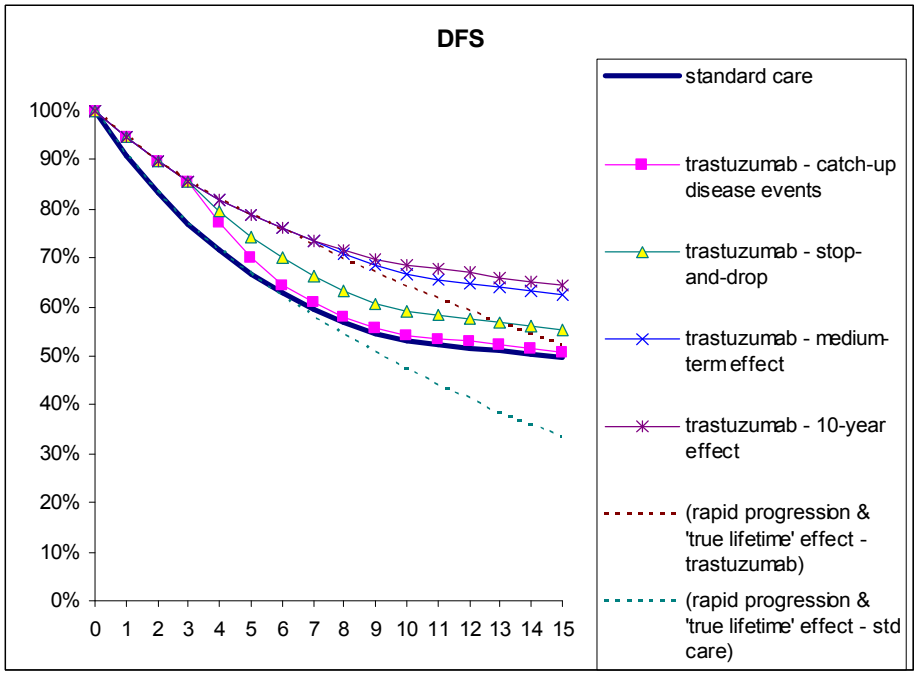


Figure: Disease-free survival in models of long-term durability with trastuzumab vs. standard care



There are arguments for long-term durability in terms of extrapolating for the experience with other breast cancer treatments as seen in the Oxford Overview[7] curves, where there may be similar likely benefits from trastuzumab-based therapy as has occurred with tamoxifen, as a result of the biology of breast cancer. It is noted however that CaTSoP (April 2006) considered that although with hormonal therapies such as tamoxifen there are good data to support extrapolation of DFS what occurred in the clinical trials, no such strong evidence exists for monoclonal antibodies.[8]

[7] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687–1717.
[8] CaTSoP (April 2006) was asked by PHARMAC staff to consider the ability to extrapolate the disease-free survival data from the HERA trial beyond two years. The Sub-Committee noted that increases in disease-free survival generally, but not always, translate into increases in overall survival when longer-term follow up data matures, although the benefit is generally smaller

The ScHARR analysis[9] modelled durability of 5 years (no further benefit of treatment beyond five years), not the four years in PHARMAC's previous modelling (TAR 75). Extended results from the combined B31 and N931 analysis of 12 months concurrent trastuzumab suggest persisting effects with one more year's data (3 years median follow-up), but there is a possible waning of effect after 3 years or earlier in the HERA, BCIRG006 and PACS04 trials (see below).

PTAC (July 2008) considered it appropriate to assume a three-year period of benefit from adjuvant trastuzumab when modelling the durability of response. The Committee considered that three years duration was the extent to which there was reliable published evidence from the clinical trial data reported to date. The Committee did not consider that modelling a five-year period benefit was appropriate (as modelled in the UK ScHARR report).

PTAC considered that some waning of treatment benefit should be included in the base case scenario of the updated CUA model, and that assumptions of either no waning of effect or different rates of waning should be modelled in sensitivity analyses.

PTAC considered that, on the balance of probability, it was most realistic to assume in the base case that the benefit of trastuzumab is not long-lasting but that some benefit would remain in the medium term. Members noted that this meant a proportion of patients treated with trastuzumab would have a lower risk of disease recurrence that continued beyond the period of benefit, but that trastuzumab-treated patients would eventually adopt the baseline risk of disease recurrence in, with no further treatment benefit.

Conversely, PTAC did not consider other options presented for waning of treatment effect to be as appropriate, including scenarios that resulted in rapid convergence or non-divergence in disease free survival curves following the period of benefit. Of note, the Committee did not consider a lifetime benefit scenario to be appropriate, where the benefits seen in the trials over the first three years are maintained indefinitely for the rest of patients' lives, so that disease-free survival curves continue to diverge.

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than for disease-free survival. Members noted that with hormonal therapies such as tamoxifen, there are good data to support such extrapolation**.** Members considered, however, that no such strong evidence exists for monoclonal antibodies.

[9] Ward S, Pilgrim H, Hind D. Trastuzumab for the treatment of primary breast cancer in HER2 positive women: a Single Technology Appraisal. University of Sheffield School of Health and Related Research (ScHARR), May 2006. http://www.nice.org.uk/page.aspx?o=328487 Update with revised cost per QALY at http://www.nice.org.uk/page.aspx?o=328530

B. Short-term durability of trastuzumab effect (intra-trial waning of effect)

The ScHARR analysis modelled durability of 5 years (no further benefit of treatment beyond five years), not the four years in PHARMAC's previous modelling (TAR 75). This is where the durability of response of sequential therapy has not been demonstrated. Since the time of PHARMAC's original CUA modelling (TAR 75), evidence is emerging of possible intra-trial wanings of effect, at least with 12 months regimens.

Although the updated results from the B31 and N931 joint analysis for 12 months concurrent treatment have indicated persisting effects with one more year's data (3 years median follow-up), there is still possible waning of effect seen after 3 years or earlier in the HERA, BCIRG006 and PACS04 trials.

The evidence for waning of effect emerged firstly with HERA (Smith et al Lancet 2007), where the 23-month median follow-up data showed the DFS HR had risen to 0.64 (RRR 36%), compared with the 12 month median follow-up HR of 0.54 (46%), this effect being insensitive to whether intention to treat of censoring. PHARMAC analysis suggests this trend is statistically significant.

The 23-month follow-up report for the HERA study included period-specific hazards by time, showing a change in disease recurrence over time, with convergence of hazards and overlapping of their confidence intervals beyond ~18 months:

Figure: Annualised DFS hazard rates, HERA one-year trastuzumab treatment vs. observation arms

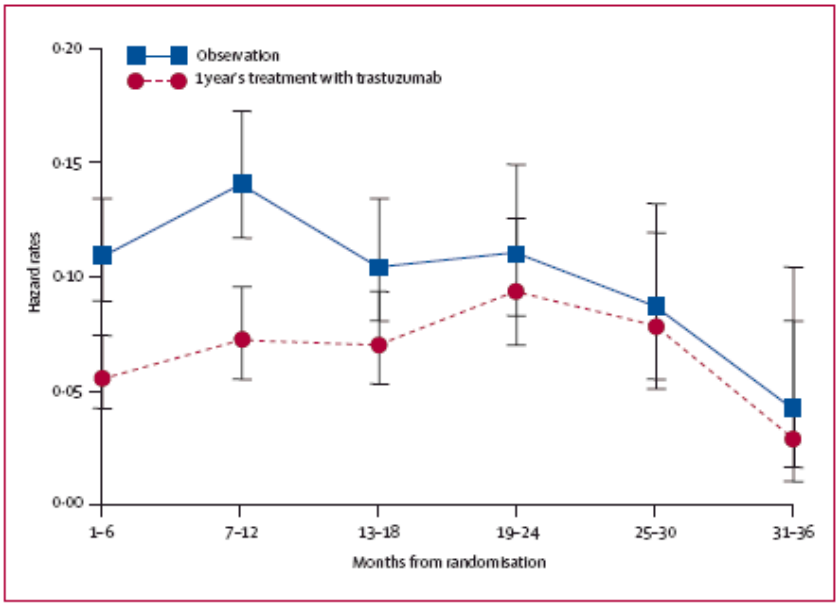


Figure 4: Annualised disease-free survival hazard rates for 1 year of trastuzumab vs observation

Source: Smith et al 2007

Ideally the reduction in DFS benefits over time in the HERA trial should be confirmed by testing proportional hazards by time.[10] However, in the absence of any available such analysis of individual patient data, the reduction in DFS benefits over time reported in the HERA trial (the 0.54 HR becoming 0.64) is statistically significant on testing for interaction by the two time periods (p=0.01, summing using study group event numbers and increments and starting intention-to-treat populations to calculate relative risks specific to the two time periods, then testing conventionally for statistical interaction (heterogeneity of treatment effect) to compare the two relative risks[11]).

HERA - 23-month vs. 12 month median follow-ups

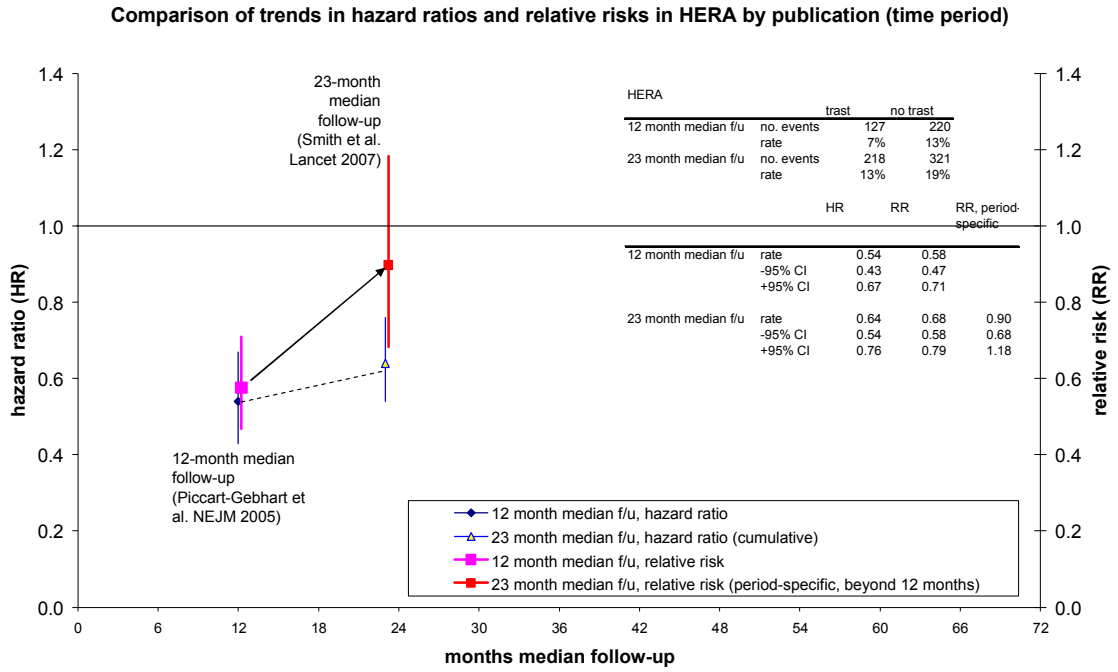
		numbers			difference		calculated relative risk (RR)			RR reduction
		trastuzumab	std tmt	total	i.e. tmt effect (ARR)	published HR (95% CI)	RR	-95% CI	+95% CI	(RRR)
outcome of interest:		disease recurrence or all-cause death								
Input data:										
12 mth f/u	n events	127	220	347						
0-12 mths	N patients	1694	1693	3387						
	%	7.5%	13.0%		5.5%	0.54 (0.43-0.67)				
23 mth f/u	n events	218	321	539						
0-23 mths	N patients	1703	1698	3401						
cumulative	%	12.8%	18.9%		6.1%	0.64 (0.54-0.76)				
calculations										
0-12 mths	n events	127	220	347						
	N patients	1694	1693	3387						
	%	7.5%	13.0%		5.5%	0.54	0.58	0.47	0.71	42.3%
	std error of %	0.6%	0.8%		0.8%					
13-23 mths	n events	91	101	192						
=23mth f/u	N patients	1703	1698	3401						
minus 12m	%	5.3%	5.9%		0.6%		0.90	0.68	1.18	10.2%
difference in treatment effects					4.9%					
approximate 95% CI for difference							4.9%	3.3%	6.5%	
log$_n$ of RR (log$_n$E) and 95%CIs; standard errors										
	0-12 mths	E_1					-0.55	-0.76	-0.34	-0.11
	13-23 mths	E_2					-0.11	-0.38	0.17	-0.14
Difference between log$_n$ relative risks										
	SE(d)						0.18			
	d[=E_1-E_2], CI(d)						-0.44	-0.79	-0.10	
Ratio of relative risks	ratio RR=exp(d), with 95%CI						0.64	0.45	0.91	
Tests of interaction										
	z value (= d/SE(d))				-2.52					
	p-value				0.012	+ve evidence of heterogeneity				

The relative risk of disease recurrence or all-cause death for (HERA - 23-month vs. 12 month median follow-ups) 0-12 mths is 0.58
The relative risk of disease recurrence or all-cause death for 13-23 mths is 0.90
The null hypothesis states that there is no difference between the relative risks for 0-12 mths and 13-23 mths
The difference between these two relative risks is 4.9% (95%CI 3.3% to 6.5%)
The ratio of these two relative risks (ratio of RR) is 0.64 (95%CI 0.45 to 0.91)
The test statistic, -2.52 gives p=0.01183 when compared to a table of the Normal distribution.
Hence it can be concluded that the evidence suggests the null hypothesis is rejected and there is a significant difference between these relative risks.

The effects of the discord between the cumulative hazard ratio reported in the 23-month HERA f/u and period-specific effects from events occurring after the 12-month interim f/u can be seen in the following graph. This demonstrates a greater waning of effects with period-specific relative risk. The similarities between the published 12-month median f/u hazard ratio (HR 0.54) and the calculated relative risk for the same time period (RR 0.58) give some comfort around the above testing for statistical interaction.

[10] Testing for proportional hazards over time will be to determine whether the effect of treatment is constant or varies significantly over time
[11] Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219. http://www.bmj.com/cgi/content/full/326/7382/219

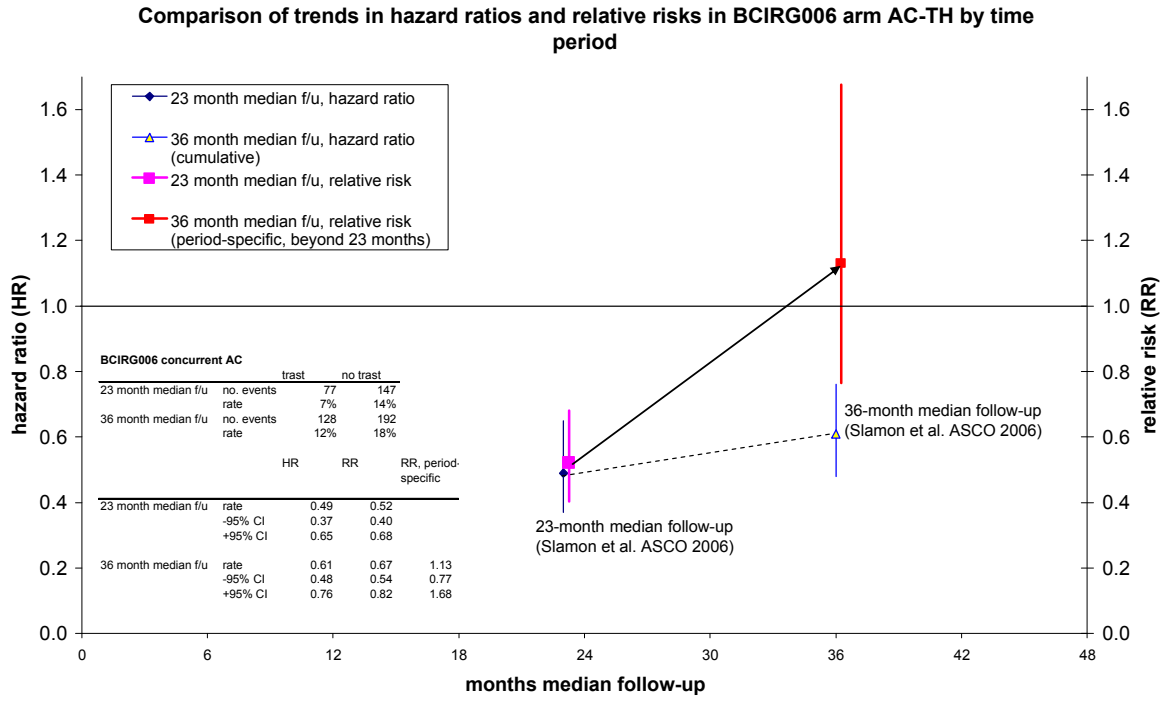
Figure: Cumulative hazard ratios and period-specific relative risks in HERA by time



Extended follow-up of the HERA study population is unlikely to quantify the sequence's long-term benefits and risks, due to the partial loss of the control arm (with potential bias from non-randomisation).

More recently, PAC04 has reported an increase trend in its HR (4 years medina follow-up 0.86 overall, but 1.04 for months 19-48 vs. 0.57 for months 0-18), although this was not statistically significant. No further data have been reported for N9831's sequential arm.

Likewise with 12 months concurrent treatment, BCIRG006 arm AC-TH appears to show a statistically-significant decline in effect, the HR increasing from 0.49 at 23 months median f/u to 0.61 at 36 months median f/u ($p < 0.01$):



BCIRG 006 concurrent anthracyclines - 36-month vs. 23 month median follow-ups

		numbers			difference		calculated relative risk (RR)			RR reduction
		trastuzumab	std tmt	total	i.e. tmt effect (ARR)	published HR (95% CI)	RR	-95% CI	+95% CI	(RRR)
outcome of interest:		disease recurrence or all-cause death								
Input data:										
23 mth f/u	n events	77	147	224						
0-23 mths	N patients	1074	1073	2147						
	%	7.2%	13.7%		6.5%	0.49				
36 mth f/u	n events	128	192	320						
0-36 mths	N patients	1074	1073	2147						
cumulative	%	11.9%	17.9%		6.0%	0.61				
calculations										
0-23 mths	n events	77	147	224						
	N patients	1074	1073	2147						
	%	7.2%	13.7%		6.5%	0.49	0.52	0.40	0.68	47.7%
	std error of %	0.8%	1.0%		1.1%					
24-36 mths	n events	51	45	96						
=36mth f/u	N patients	1074	1073	2147						
minus 23m	%	4.7%	4.2%		-0.6%		1.13	0.77	1.68	-13.2%
difference in treatment effects					7.1%					
approximate 95% CI for difference							7.1%	4.9%	9.3%	
$\log_n$ of RR ($\log_n E$) and 95%CIs; standard errors										
	0-23 mths	E_1					-0.65	-0.91	-0.39	-0.13
	24-36 mths	E_2					0.12	-0.27	0.52	-0.20
Difference between $\log_n$ relative risks										
	SE(d)						0.24			
	d[=E_1-E_2], CI(d)						-0.77	-1.24	-0.30	
Ratio of relative risks	ratio RR=exp(d), with 95%CI						0.46	0.29	0.74	
Tests of interaction										
	z value (= d/SE(d))				-3.21					
	p-value				0.001	+ve evidence of heterogeneity				

The relative risk of disease recurrence or all-cause death for (BCIRG 006 concurrent anthracyclines - 36-month vs. 23 month median follow-ups) 0-23 mths is 0.52
The relative risk of disease recurrence or all-cause death for 24-36 mths is 1.13
The null hypothesis states that there is no difference between the relative risks for 0-23 mths and 24-36 mths
The difference between these two relative risks is 7.1% (95%CI 4.9% to 9.3%)
The ratio of these two relative risks (ratio of RR) is 0.46 (95%CI 0.29 to 0.74)
The test statistic, -3.21 gives p=0.00134 when compared to a table of the Normal distribution.
Hence it can be concluded that the evidence suggests the null hypothesis is rejected and there is a significant difference between these relative risks.

By contrast, HRs in the joint analysis of B31 and N9831 concurrent trials for DFS remain unchanged (0.48 at 2 years median f/u, 0.49 at 3 years, p = 0.16).

Combining raw numbers of events, the concurrent 12 month regimes (B31, N9831 concurrent, BCIRG006 concurrent anthracyclines) appear to show an overall decline in effect at three years compared with two years median follow-up (relative risk 0.52 vs. 0.77, p = 0.004, summing event numbers, increments and intention-to-treat populations to calculate crude overall relative risks specific to the two time periods, then testing conventionally for statistical interaction (heterogeneity of treatment effect) to compare the two relative risks[12]):

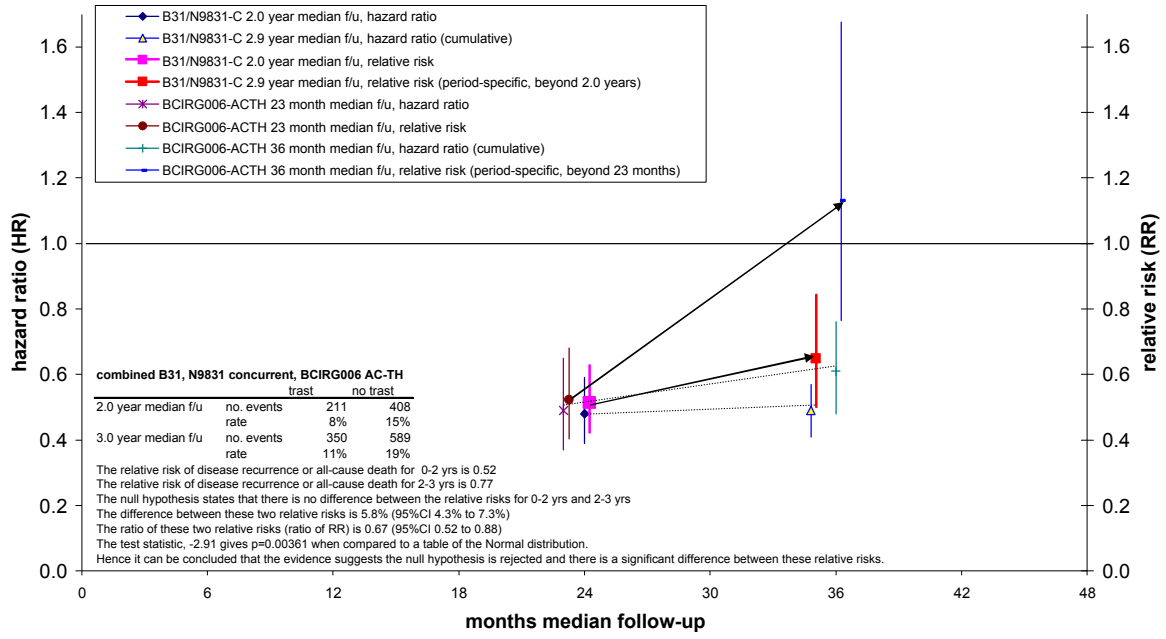
combined N9831 concurrent, B31 and BCIRG 006 concurrent AC: 3-year vs 2-year median follow-ups

		numbers			difference	calculated relative risk (RR)				RR reduction
		trastuzumab	std tmt	total	i.e. tmt effect (ARR)	published HR (95% CI)	RR	-95% CI	+95% CI	(RRR)
outcome of interest:		disease recurrence or all-cause death								
Input data:										
2 year f/u	0-2 years									
B31/N9831	n events	134	261							
	N patients	1672	1679			0.48 (0.39-0.59)				
	%	8.0%	15.5%		7.5%	0.48	0.52	0.42	0.63	48.4%
BCIRG006	n events	77	147							
	N patients	1074	1073			0.49 (0.37-0.65)				
	%	7.2%	13.7%		6.5%	0.49	0.52	0.40	0.68	47.7%
3 year f/u	0-3 years									
B31/N9831	n events	222	397							
	N patients	1979	1989			0.49 (0.41-0.57)				
	cumulative %	11.2%	20.0%		8.7%	0.49	0.56	0.48	0.65	43.8%
BCIRG006	n events	128	192							
	N patients	1074	1073			0.61 (0.48-0.76)				
	cumulative %	11.9%	17.9%		6.0%	0.61	0.67	0.54	0.82	33.4%
calculations										
0-2 yrs	n events	211	408	619						
	N patients	2746	2752	5498						
	%	7.7%	14.8%		7.1%		0.52	0.44	0.61	48.2%
0-3 yrs	*n events*	*350*	*589*	*939*						
	N patients	*3053*	*3062*	*6115*						
	cumulative %	*11.5%*	*19.2%*		*7.8%*		*0.60*	*0.53*	*0.67*	*40.4%*
2-3 yrs	n events	139	181	320						
=3yr f/u	N patients	3053	3062	6115						
minus 2yrs	%	4.6%	5.9%		1.4%		0.77	0.62	0.96	23.0%
difference in treatment effects					5.8%					
approximate 95% CI for difference							5.8%	4.3%	7.3%	
$\log_n$ of RR ($\log_n E$) and 95%CIs; standard errors										
	0-2 yrs	E_1					-0.66	-0.81	-0.50	-0.08
	2-3 yrs	E_2					-0.26	-0.48	-0.05	-0.11
Difference between $\log_n$ relative risks										
	SE(d)						0.14			
	d [=E_1-E_2], CI(d)						-0.40	-0.66	-0.13	
Ratio of relative risks		ratio RR=exp(d), with 95%CI					0.67	0.52	0.88	
Tests of interaction										
	z value (= d/SE(d))				-2.91					
	p-value				0.004	+ve evidence of heterogeneity				

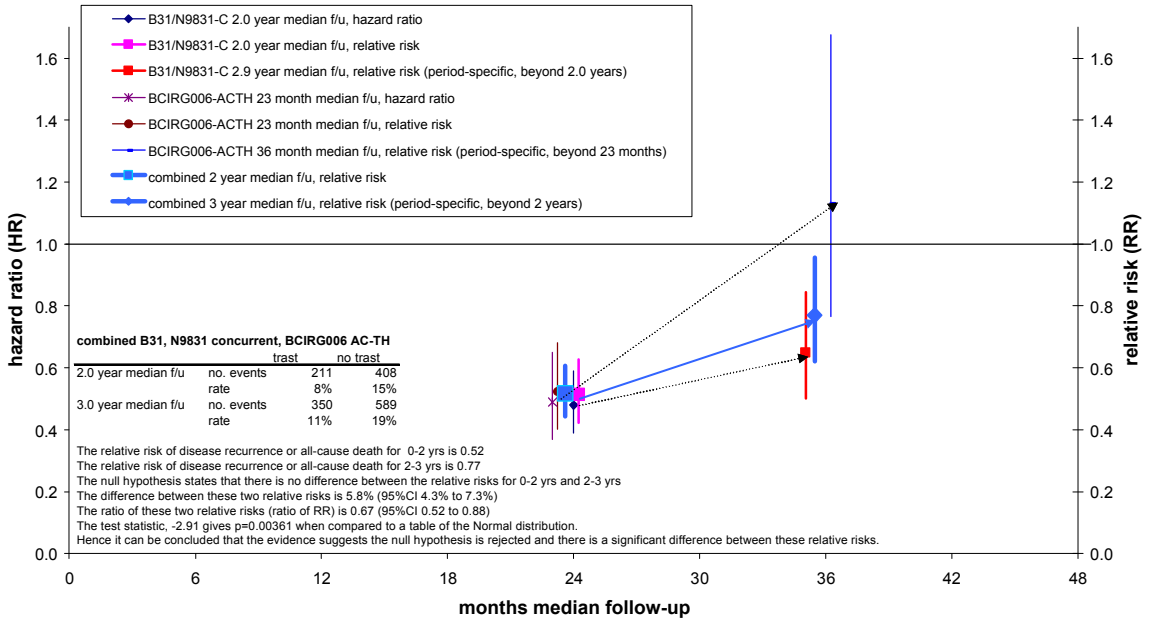
The relative risk of disease recurrence or all-cause death for (combined N9831 concurrent, B31 and BCIRG 006 concurrent AC: 3-year vs 2-year median follow-ups) 0-2 yrs is 0.52
The relative risk of disease recurrence or all-cause death for 2-3 yrs is 0.77
The null hypothesis states that there is no difference between the relative risks for 0-2 yrs and 2-3 yrs
The difference between these two relative risks is 5.8% (95%CI 4.3% to 7.3%)
The ratio of these two relative risks (ratio of RR) is 0.67 (95%CI 0.52 to 0.88)
The test statistic, -2.91 gives p=0.00361 when compared to a table of the Normal distribution.
Hence it can be concluded that the evidence suggests the null hypothesis is rejected and there is a significant difference between these relative risks.

[12] Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219. http://www.bmj.com/cgi/content/full/326/7382/219

Trends in hazard ratios and relative risks by time period in trials of 12 month concurrent trastuzumab (NSABP-B31 / NCCTG-N9831 concurrent arm, BCIRG006 arm AC-TH)



Trends in overall relative risks by time period in trials of 12 month concurrent trastuzumab (NSABP-B31 / NCCTG-N9831 concurrent arm, BCIRG006 arm AC-TH)



FinHer has yet to report further follow-up data beyond the interim 3-year median follow-up results. There is no evidence of statistically significant changes in effect over these three years.

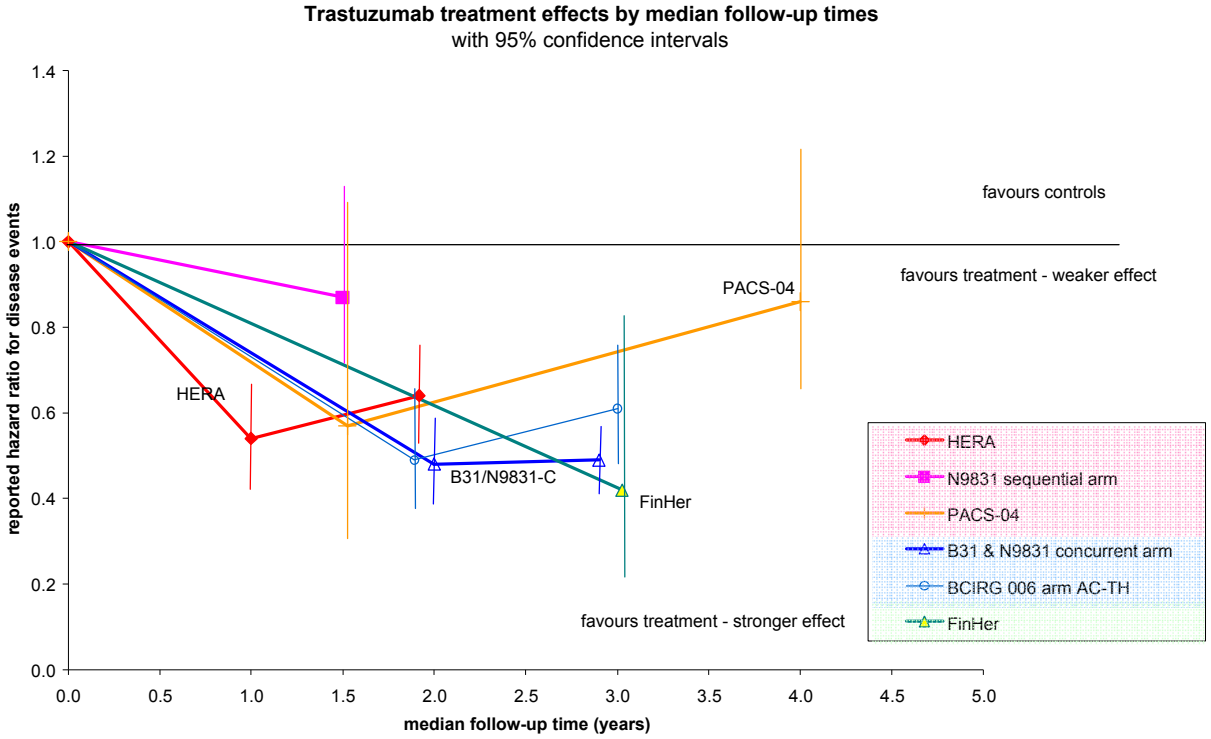
Trends in HRs for disease events by median follow-up time can be seen in the following table and graph (with 95% CIs for individual HRs, but no CIs given for rate ratios by time):

Table: Absolute risk reductions, and HRs (with 95%CIs) for adjuvant trastuzumab trials

Disease free survival

	Year of median follow-up (approximate)			
Trial	**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: Trends in HRs with 95% CIs for disease events by median follow-up time for individual trials



Notes to figure:

- The effectiveness of 12 months concurrent appears to significantly decline in effect over time, as does sequential. HERA was the first to show a possible waning of effect, where the hazard ratio increased significantly from 0.54 at 12 months median follow-up interim analysis to 0.64 at 23 months, p =0.01.

- A similar pattern appears for 12 months concurrent treatment, with apparent statistically-significant decline in effect for BCIRG006 arm AC-TH (HR 0.49 at 23 months median f/u, 0.61 at 36 months median f/u; $p < 0.01$. Although by contrast the HRs for the joint analysis of trials B31 and N9831 concurrent 12 month treatment indicate that DFS remained unchanged over the same time (0.48 at 2 years median f/u, 0.49 at 3 years, $p = 0.16$), extending to combined all trials of concurrent 12 month regimes (B31, N9831 concurrent, BCIRG006 concurrent anthracyclines) appear to show an overall decline in effect at three years compared with two years median follow-up (incremental relative risks 0.52 vs. 0.77, $p = 0.004$). In short, the significant waning of effect in BCIRG006 appears to dominate the lack of decline (maintained effect) in B31/N9831-concurrent joint analysis, suggesting that the effects of 12 month concurrent treatment too wanes with time.

- FinHer (concurrent 9 weeks treatment) has yet to report further follow-up data beyond its interim 3-year median follow-up results. There is no evidence of statistically significant changes in effect over these three years.

These patterns suggest apparent significant waning of effects with the HERA and BCIRG 006 trials but not for other concurrent regimens (B31/N9831 concurrent arm, FinHer). Combined, the concurrent 12 month regimes (B31, N9831 concurrent, and BCIRG006 concurrent anthracyclines) appear to show an overall decline in effect at three years compared with two years median follow-up. Further discussion of durability of response was contained in Appendix Four to PHARMAC's article in the NZ Medical Journal in July 2007 (pages 21 to 25).

CaTSoP (June 2008) noted that the benefits of trastuzumab treatment in the HERA study had decreased over time, whereas the benefits in the combined data from NCCTG N9831 and NSABP B-31 were maintained. Members considered that it was too early to say if the early benefits seen for trastuzumab were durable long term. The Subcommittee considered that further follow-up data from all studies were necessary to determine the durability of efficacy for trastuzumab treatment; however, members noted that longer-term data may be confounded by cross-over in some of the studies.

PTAC (July 2008) considered that, overall, the data reported to date for trastuzumab in HER2-positive early breast cancer demonstrated no statistically significant benefit of 12 months sequential trastuzumab in N9831 over 18 months median follow-up and PACS04 over four years median follow-up; an apparent waning of benefit with 12 months sequential trastuzumab in HERA over two years and 12 months concurrent trastuzumab in BCIRG 006 over three years; and maintained benefit for the 12 months concurrent trastuzumab in B31/N9831 combined over three years. Members noted that FinHer, the trial of the nine weeks concurrent regimen, has yet to report further follow-up data beyond the 3-year median follow-up results.

Durability of effect used in the updated PHARMAC CUA

With the above information in mind, modelling the durability of response assumes a three-year period of benefit from adjuvant trastuzumab, being the median follow-up extent to which there is reliable published evidence from the clinical trial data reported to date for 12 month and nine week concurrent treatments. This in effect is an optimistic assumption for 12 months sequential, as the positive HERA data extend for only 23 months median follow-up.

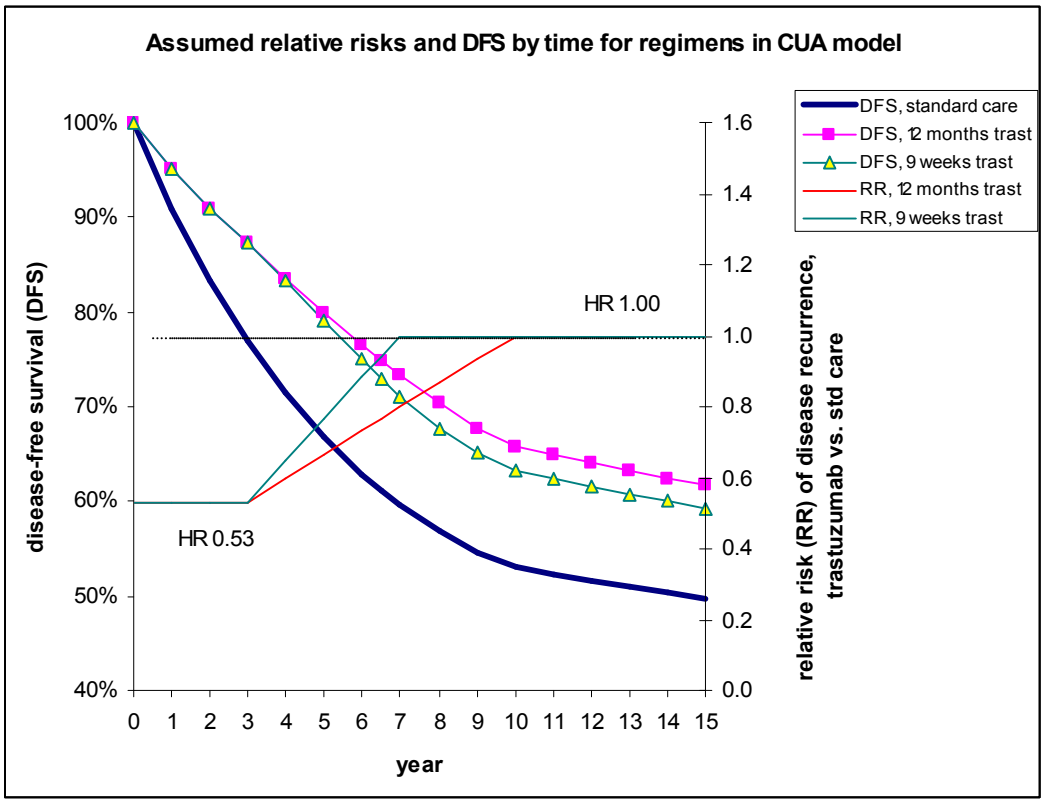
Some long-term waning of treatment benefit is included in the base case scenario of the updated CUA model, and assumptions of either no waning of effect or different rates of waning are modelled in sensitivity analyses.

For long-term durability, base case modelling assumes a medium-term benefit scenario, where some benefit remains up to 10 years. This assumes a proportion of patients treated with trastuzumab will have a lower risk of disease recurrence that continues beyond the period of benefit, but that the relative risk of disease progression in trastuzumab-treated patients moves towards 1.0 over time – where reaching a relative risk of 1.0 means the treatment group eventually adopts the baseline risk for disease recurrence, with no further treatment benefit. The extent of waning in the intervening years 4 to 9 depends on the regimen:

- For 12 months concurrent and sequential regimens, modelling assumes relative risks reach 1.0 at year 10 (i.e. 7 years after the end of the period-of-full-benefit).

- For the nine weeks concurrent regimen, modelling assumes relative risks deteriorate faster to reach 1.0 at year 6-7 (i.e. 3.5 years after the end of the period-of-full-benefit).

Relative risks for disease events and consequent DFS are therefore modelled over time for treatment regimens as follows:



For short-term durability, base case modelling conservatively assumes no intra-trial waning of effect, using constant risk reductions over the period of benefit. This is despite the above evidence that such waning has occurred in trials of, and appears to be statistically significant overall for, both 12 month sequential and 12 month concurrent regimens. No data are available for nine week concurrent treatment.

Note that although not used for short-term durability, the above likelihoods of significant waning during the period of benefit therefore do lend weight to the use of the medium-term benefit scenario (with the relative risk moving to eventually reach 1.0) to extrapolated for long-term durability beyond the period of benefit, rather than a lifetime benefit effect scenario.

Annex Four

Cardiotoxicity with trastuzumab

The previous CUA (TAR 75 August 2006) used cardiac events rates derived from the HERA trial. However, any analysis looking more broadly including 12 month concurrent treatments needs to account for the higher rates seen in the concurrent trials (e.g. N9831/B31), where long-term cardiotoxic effects from adjuvant trastuzumab treatment affect cost utility analysis modelling.

The Appendix Six to the previous TAR 75 had noted that that the concurrent treatment regimens used in N9831 (arm C) and NSABP B31 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 suggested 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.

Based on relevant material published since mid 2007 on cardiotoxicity, including reversibility,[13] [14] [15] [16] [17] [18] the table below shows the prevalence (number of cases) of cardiotoxicity published in the key clinical trial reports for the three trastuzumab regimens compared with chemotherapy alone (standard care):

Trial and treatment regimen	LVEF at baseline	significant difference	Prevalence of decrease LVEF (cases) after trastuzumab	Prevalence of severe CHF** (cases) after trastuzumab
HERA (12 months sequential post AC)	>55% post –AC	≥10% to < 50%	+4.9% (79)	0.5% (9)
B31 (12 months concurrent post AC)	>50% post –AC	≥10% to < 50%	+17% (3 year cumulative rate)	3.3% (27) Up to 20% if LVEF 50-54% and age >50y
N9831 (12 months sequential post AC) and (12 months concurrent post AC)	>50% post -AC		Not reported Not reported	+2.2% (15) +2.9% (20)

[13] Suter TM, Procter M, van Veldhuisen DJ, Muscholl M, Bergh J, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol. 2007 Sep 1;25(25):3859-65.
[14] Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, 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 Mar 10;26(8):1231-8. http://jco.ascopubs.org/cgi/content/full/26/8/1231
[15] Ewer MS, Lenihan DJ. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground? J Clin Oncol. 2008 Mar 10;26(8):1201-3. http://jco.ascopubs.org/cgi/content/full/26/8/1201
[16] Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol. 2007 Aug 10;25(23):3525-33.
[17] Sengupta PP, Northfelt DW, Gentile F, Zamorano JL, Khandheria BK. Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. Mayo Clin Proc. 2008 Feb;83(2):197-203.
[18] McArthur HL, Chia S. Cardiotoxicity of trastuzumab in clinical practice. N Engl J Med. 2007 Jul 5;357(1):94-5. http://content.nejm.org/cgi/content/full/357/1/94

BCIRG006 (12 months concurrent post AC)	>50% post -AC	>15% to <50%	+2.0% (21)	+1.6%
FinHer (9 weeks concurrent, pre-AC)	>50% post - surgery*	≥10% to < 50%	-3% (3) (not statistically significant)	-1% (1)

* PHARMAC staff have previously estimated that 15-20% more patients could be treated with the 9 weeks regimen, if given as per the FinHer protocol, because treatment with trastuzumab occurs before cardiotoxic anthracycline treatment.
**As classified NYHA class 3 or 4 congestive heart failure

Note however that that differing methods for measuring cardiac function, different classifications of cardiac dysfunction and dissimilar treatment protocols for the management of these patients in these trials mean that the true prevalence and clinical importance of trastuzumab-associated cardiotoxicity cannot be accurately determined. PTAC has considered the 12 month concurrent treatment regimen has a higher risk of cardiotoxicity than the other treatment regimens, however the cardiotoxicity appears to be manageable through cessation of trastuzumab and pharmaceutical treatment. Therefore the modelled effects of cardiotoxicity have been limited to treatment to rectify cardiac dysfunction, and have assumed no long term effect for these patients. In addition, the Committee considered that the prevalence of cardiac adverse effects in clinical practice may be higher than that seen in the clinical trials, because patients who receive treatment in clinical practice may not be as healthy as the trial participants (who had to meet strict inclusion criteria).

As has been previously described in TAR 75b, the FinHer trial did not show any increase in cardiac adverse effects in patients treated with trastuzumab, but this trial was underpowered to detect differences in cardiac safety. Therefore, although the cardiac adverse event rates are lower in FinHer (and may be expected to be lower in clinical practise for a number of pharmacological reasons), the updated CUA assumes that patients treated with nine weeks of concurrent trastuzumab have the same risk of developing cardiac adverse effects as the 12 months sequential regimen. This disfavours the cost-effectiveness of the nine week regimen.

CaTSoP (June 2008) considered that trastuzumab treatment was associated with an increased risk of cardiotoxicity, although members considered that evidence to date indicated that this cardiotoxicity was generally manageable and reversible. However, members commented that the assessment tools for cardiotoxicity used in the trials were crude, for example a patient has generally lost a considerable degree of heart function before it can be detected on an ECHO cardiogram and normal echocardiograms frequently occur in patients in heart failure. Therefore, members considered that although diagnostic testing appeared to show reversibility of trastuzumab-associated cardiotoxicity clinically, patients' hearts may not have returned to normal. Members noted that the longer term risks of trastuzumab associated cardiotoxicity were still unknown.

Modelling cardiotoxicity

Patients with sufficient heart function

The trials of 12 months trastuzumab initiated trastuzumab treatment after completion of anthracycline chemotherapy, which is known to be cardiotoxic. In these trials, a number of patients who had met inclusion criteria for the trial and were randomised to receive trastuzumab subsequently did not receive treatment because of insufficient heart function post cardiotoxic anthracycline chemotherapy.

The FinHer regimen administers trastuzumab prior to cardiotocxic chemotherapy. PHARMAC staff have previously estimated that 15-20% more patients could receive trastuzumab with the nine week concurrent regimen than the longer duration regimens, if given as per the FinHer protocol.[19] This difference in patient numbers has not been captured by the current model, which is a conservative assumption (favours 12 months treatment).

Rates of cardiotoxicity used in the model

PTAC (July 2008) considered that the different rates of cardiotoxicity with the different regimens are clinically important and should be included in the updated cost-utility analyses. The Committee considered that in clinical practice there may be higher rates of cardiotoxicity than those reported in

[19] 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

the clinical trials, due to less stringent cardiac exclusion criteria and monitoring being applied to patients in clinical practice compared with those applied in the clinical trials, and that this should be considered in the CUA. The Committee considered that it would be acceptable at this stage, for the specific purpose of CUA modelling, to assume that the majority of the cardiac side effects were manageable on cessation of trastuzumab treatment with some cases requiring ongoing other long term treatment. The Committee considered at this stage it would not be unreasonable for the updated CUA itself to assume no appreciable long term clinical consequences from trastuzumab-associated cardiotoxicity.

The clinical trials for 12 months of trastuzumab treatment (concurrent or sequential) reported significant increases in symptomatic congestive heart failure and severe cardiac adverse events in patients treated with trastuzumab compared with standard care. In the model, these adverse effects (symptomatic heart failure and severe cardiac events) were assumed to occur at the same rate as reported in the clinical trials for the treatment regimens (rates incremental those reported for standard care). The cumulative incremental rates of symptomatic heart failure and severe cardiac adverse events are shown in the table below.

Treatment regimen	Symptomatic congestive heart failure	Severe cardiac adverse effects
12 months sequential post AC	1.13%	0.54%
12 months concurrent post AC	6%	3%
9 weeks concurrent pre-AC	1.13%	0.54%

The FinHer trial did not report an increased incidence of cardiac toxicity (in fact there were less cardiac events in the trastuzumab than the standard care arm). The FinHer paper states that the addition of trastuzumab was not associated with an increased frequency of adverse effects related to docetaxel or vinorelbine. However, because FinHer's small sample size may mean it is underpowered to detect and measure cardiac toxicity and other adverse effects; in addition, FinHer used relatively low cumulative doses of anthracycline chemotherapy (180 mg/m^2 epirubicin versus the maximum tolerated cumulative dose of 720mg/m^2 and more cardiotoxic doxorubicin use in the B31/N9831 studies at a cumulative dose of 240 mg/m^2 (maximum tolerated cumulative dose 500 mg/m^2), and had perhaps less sensitive LVEF testing/thresholds. Previously (in TAR75b) it was assumed that adverse effects in the nine weeks concurrent regimen would occur at the same rate as in the 12 months sequential model, for the first six months of treatment. Effectively meaning the incidence of adverse effects was reduced by half compared with the 12 months sequential model. The current model assumes the rate of adverse effects for the concurrent nine weeks regimen is the same as the incidence reported for the 12 months sequential regimen. This assumption is conservative, and disfavours the nine week concurrent trastuzumab regimen.

It should be noted that asymptomatic decreases in LVEF were not modelled for this analysis because these are not classified as severe, would potentially not be identified in clinical practice due to the asymptomatic nature, and appear to be reversible on cessation of treatment. If the prevalence of asymptomatic decreases in LVEF, and a treatment protocol for the management of this condition, was included in the analysis this would disfavour the concurrent 12 months regimen (in the NSABP-B31 trial 34% of patients treated with trastuzumab experienced decreases in LVEF, compared with 17% of patients in the standard chemotherapy arm).

PTAC (July 2008) considered that the CUA model should consider the effect of an increased rate of cardiotoxicity, to reflect that it is likely that some patients treated in clinical practice in New Zealand would have poorer baseline heart function and pose higher risk for cardiotoxicity (these patients would not have met the strict inclusion criteria for the clinical trials). As this assumption disfavours trastuzumab, especially the 12 months concurrent regimen, an increased incidence of cardiotoxicity is modelled in the sensitivity analysis rather than the base case.