



PHARMAC funding of 9-week concurrent trastuzumab (Herceptin) for HER2-positive early breast cancer

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Abstract

A 9-week regimen of trastuzumab (Herceptin®) given concurrently with a taxane will be funded for HER2-positive early breast cancer patients in New Zealand.

The use of trastuzumab in this population has been investigated in sequential (after chemotherapy) or concurrent (with taxane chemotherapy) settings. Five RCTs have been reported—HERA, NSABP B31, NCCTG N9831, BCIRG 006, and FinHer. Uncertainty persists about optimal regimen duration, dose and sequencing, how to minimise cardiotoxicity, and long-term clinical outcomes.

The evidence for the 9-week concurrent regimen was sufficient to justify funding. This regimen has shown results comparable to longer duration treatments; allows more patients to be treated; is relatively cost-effective; and DHBs have indicated they can provide sufficient ancillary support services.

Longer duration regimens remain unfunded because of uncertainty surrounding long term clinical benefits and risks; the high cost; effects on DHB services; and their consequential unfavourable relative cost effectiveness. New data—from the sequential treatment arm of trial N9831, showing benefits that were small and statistically non-significant, and the HERA 23-month follow-up, suggesting a waning in efficacy with time—have since cast further doubt on the extent and durability of the sequential 12-month regimen's efficacy.

DHBs and PHARMAC remain open to funding longer duration regimens if cost effectiveness improves significantly and budget/resource implications become acceptable. PHARMAC has committed to international efforts (the SOLD trial) to resolve questions of optimal treatment duration.

From 1 July 2007, trastuzumab (Herceptin®) will be funded in New Zealand for the treatment of HER2-positive early breast cancer. Funding will be available for patients receiving trastuzumab when administered for 9 weeks concurrently with taxane chemotherapy. Docetaxel will also be funded for early breast cancer when given concurrently with trastuzumab.

Last year the *Journal* published a Special Series article and related correspondence about the use of trastuzumab in HER2-positive early breast cancer.^{1,2,3} Since then, in July 2006, district health boards (DHBs) and PHARMAC decided not to fund trastuzumab as a 12-month sequential regimen at that time,* but committed to ongoing active review of the evidence. After considering further evidence and following consultation, PHARMAC and DHBs have decided to fund a 9-week concurrent trastuzumab regimen.

We describe some of the background and reasoning behind PHARMAC's decisions.

HER2-positive breast cancer and trastuzumab

Human epidermal growth factor receptor 2 protein (HER2/*neu*)-positive (IHC 3+ or FISH positive) breast cancers are aggressive tumours accounting for ~15-20% of early breast cancers. Trastuzumab (Herceptin) is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to the extracellular domain of the HER2 protein on the surface of breast cancer cells. [Appendix 1](#) further describes Her2/*neu* overexpression/amplification in breast cancer and its treatments, including trastuzumab.

HER2-positive breast cancer affects 340–400 new patients in New Zealand each year. There are important regional variations in the extent of testing for HER2-positivity, and Maori and Pasifika women tend to present with later disease. [Appendix 2](#) describes aspects of the epidemiology of HER2-positive early breast cancer in New Zealand.

Trastuzumab is registered in New Zealand⁴ for the treatment of patients with metastatic HER2-positive breast cancer, and also has provisional approval for the treatment of HER2-positive early breast cancer following surgery and completion of adjuvant chemotherapy; this latter indication is based on the results of, and the treatment regimen used in, the HERA phase III clinical trial.⁵

Trastuzumab has been funded by DHBs for HER2-positive metastatic breast cancer since 2002, and is available through DHB hospitals.† The funding of trastuzumab and taxanes (paclitaxel and docetaxel) for metastatic breast cancer resulted from PHARMAC taking over management of the ‘Cancer Basket’ of oncology medicines; these medicines were determined by the Ministry of Health and DHBs and did not undergo formal clinical or economic assessment by PHARMAC.

Trastuzumab for HER2-positive early breast cancer—treatment regimens and available trial data

To date, adjuvant treatment of HER2-positive early breast cancer with trastuzumab has been investigated in two broad treatment regimens:

1. ‘sequential treatment’—trastuzumab for 12 months following completion of chemotherapy (anthracycline ± taxane);
2. ‘concurrent treatment’—trastuzumab for 9–10 weeks, or 12 months, started in combination with taxane chemotherapy (either preceding or following completion of anthracycline chemotherapy).

There have been five open-label randomised controlled trials (RCTs) reporting outcomes for adjuvant trastuzumab against standard treatment in HER2-positive early breast cancer to date⁶—HERA⁷ (12-month sequential), NSABP B31^{8,9} (12-month concurrent post-anthracycline), NCCTG N9831^{10,11} (12-month sequential, or 12-month concurrent post-anthracycline), BCIRG 006¹¹ (12-month concurrent), and FinHer¹² (9-week concurrent pre-anthracycline).‡ Specific regimes studied in the trials are briefly as follows (detailed in [Appendix 3](#)):

- HERA—a three-arm open-label RCT comparing 12 months and 24 months sequential with standard chemotherapy:
 - **control (n=1693-1698§):** *Observation alone following completion of standard neoadjuvant or adjuvant chemotherapy*

- **1 Year arm (n=1694-1703§):** 12 months sequential trastuzumab treatment following completion of standard neoadjuvant or adjuvant chemotherapy
- **2 Year arm (n=1694-1701§):** 24 months sequential trastuzumab treatment following completion of standard neoadjuvant or adjuvant chemotherapy
- NCCTG N9831—a three-arm open-label RCT comparing sequential and concurrent trastuzumab treatment with standard chemotherapy:
 - **Arm A (control) (n= 979):** 4 cycles of AC treatment followed by 12 weeks paclitaxel
 - **Arm B (12 months sequential trastuzumab treatment) (n=985):** 4 cycles of AC treatment followed by 12 weeks paclitaxel and then 52 weeks trastuzumab
 - **Arm C (12 months concurrent trastuzumab treatment) (n=840):** 4 cycles AC followed by 12 weeks paclitaxel; trastuzumab started on day 1 of paclitaxel and continued for 12 months.
- NASBP B31—a two-arm open-label RCT comparing concurrent trastuzumab treatment with standard chemotherapy:
 - **Control (n=1024):** 4 cycles of AC treatment followed by 12 weeks paclitaxel
 - **12 months concurrent trastuzumab treatment (n=1019):** 4 cycles AC followed by 12 weeks paclitaxel; trastuzumab started on day 1 of paclitaxel and continued for 12 months
- BCIRG 006—a three-arm open-label RCT comparing concurrent trastuzumab treatment (with 2 different chemotherapy regimens) with standard chemotherapy:
 - **Arm AC-T (control) (n=1073):** 4 cycles of AC treatment followed by 4 cycles docetaxel
 - **Arm AC-TH (12 months concurrent trastuzumab) (n=1074):** 4 cycles of AC treatment followed by 4 cycles docetaxel; trastuzumab started on day 1 of docetaxel and continued for 12 months
 - **Arm TCH (12 months concurrent trastuzumab) (n=1075):** 6 cycles docetaxel and carboplatin; trastuzumab started on day 1 of docetaxel/carboplatin and continued for 12 months
- FinHer—an open-label RCT comparing docetaxel with vinorelbine for the adjuvant treatment of early breast cancer (n=1010). For the subset of women with HER2-positive cancers (n=232), patients were further randomised to four arms comparing concurrent trastuzumab (with 2 different chemotherapy regimens – docetaxel or vinorelbine) with docetaxel or vinorelbine chemotherapy alone:
 - **docetaxel + FEC, no trastuzumab (n=58):** 3 cycles of docetaxel followed by 3 cycles of AC
 - **docetaxel + FEC, trastuzumab (n=54):** 3 cycles of docetaxel followed by 3 cycles of AC; trastuzumab started on day 1 of docetaxel and continued for 9 weeks
 - **vinorelbine + FEC, no trastuzumab (n=58):** 3 cycles of vinorelbine followed by 3 cycles of AC
 - **vinorelbine + FEC, trastuzumab (n=62):** 3 cycles of vinorelbine followed by 3 cycles of AC; trastuzumab started on day 1 of vinorelbine and continued for 9 weeks

The design and some results from these trials are summarised on the bpac^{nz} website (<http://www.bpac.org.nz/magazine/2007/april/herceptin.asp>), Adjuvant! online (<http://www.adjuvantonline.com/breasthelp0306/Trastuzumab.html>) and in the tables in Appendix 3, with the following table and figures summarising the primary efficacy results in terms of disease-free survival (DFS):

Table 1. Hazard ratios and absolute improvements in DFS by trial and regimen type and across studies (PHARMAC analysis)

Trial	Sequential (trastuzumab post taxane) [n tmt/N tmt vs. n obs/N obs], hazard ratio (95% CI), % absolute improvement ¹ (minimal from 95% CI ¹)	Concurrent (trastuzumab with taxane) [n tmt/N tmt vs. n obs/N obs], hazard ratio (95% CI), % absolute improvement ¹ (minimal from 95% CI ¹)
(HERA one-year treatment arm, 12 mth f/up–interim result)	[127/1694 vs. 220/1693], 0.54 (0.43-0.67), 5.5%	
HERA one-year treatment arm, 23 mth median f/up	[218/1703 vs. 321/1698], 0.64 (0.54-0.76), 6.1% (3.9%)	
NSABP B31		[83/864 vs. 171/872], 0.45 (CI not reported; 2P=10 ⁻⁹), 10.0% (7.3%)
NCCTG N9831	[103/985 vs. 117/979], 0.87 (0.67-1.13), 1.5% (-1.5%)	[50/808 vs. 90/807], 0.55 (CI not reported; 2P=0.0004), 5.0% (2.5%)
joint analysis of N9831/B31		[134/1672 vs. 261/1679], 0.48 (0.39-0.59), 7.5% (5.8%)
BCIRG 006 Arm AC-TH (36 mth year f/u)		[128/1074 vs. 192/1073], 0.61 (0.48-0.76), 6.0% (3.2%)
Overall post-anthracycline treatment	[321/2688 vs. 438/2677], 0.70 (0.61-0.81), 4.4%² (2.7%)	[262/2291 vs. 453/2235], 0.53 (0.46-0.62), 6.9%² (5.5%)
FinHer (pre-anthracycline treatment) 36 mth f/u–interim		[12/115 vs. 27/116], 0.42 (0.21-0.83), 12.8% (3.7%)
non-anthracycline, concurrent (BCIRG 006 Arm TCH), 36 mth		[142/1075 vs. 192/1073], 0.67 (0.54-0.83), 4.7% (1.8%)

Notes:

1. Absolute improvements in DFS are the differences between rates of disease recurrence in the observation and treatment arms. Minimum absolute improvements derive from upper limits of 95% confidence intervals for calculated DFS relative risks.
2. Overall results for sequential treatment comprise the N9831 sequential (B) and HERA one year trastuzumab arms compared with respective control groups (HERA 2-year median follow-up results).
3. Overall results for concurrent treatment comprise N9831 concurrent (C), NSABP B31 trastuzumab and BCIRG 006 AC-TH arms compared with respective control groups. These results are post-anthracyclines, and hence do not include concurrent treatment given in FinHer (pre-anthracyclines), nor the non-anthracycline (carboplatin + docetxel + trastuzumab) Arm TCH of BCIRG 006.

Figure 1. Hazard ratios for disease recurrence by trial and regimen type and across studies (PHARMAC analysis)

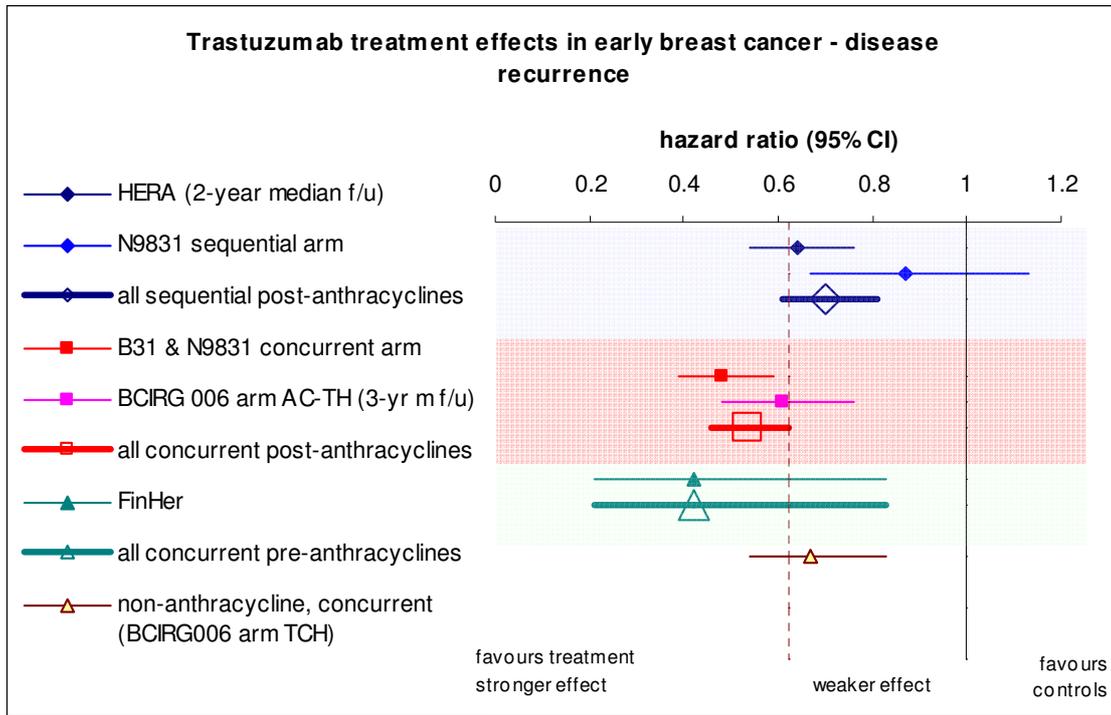
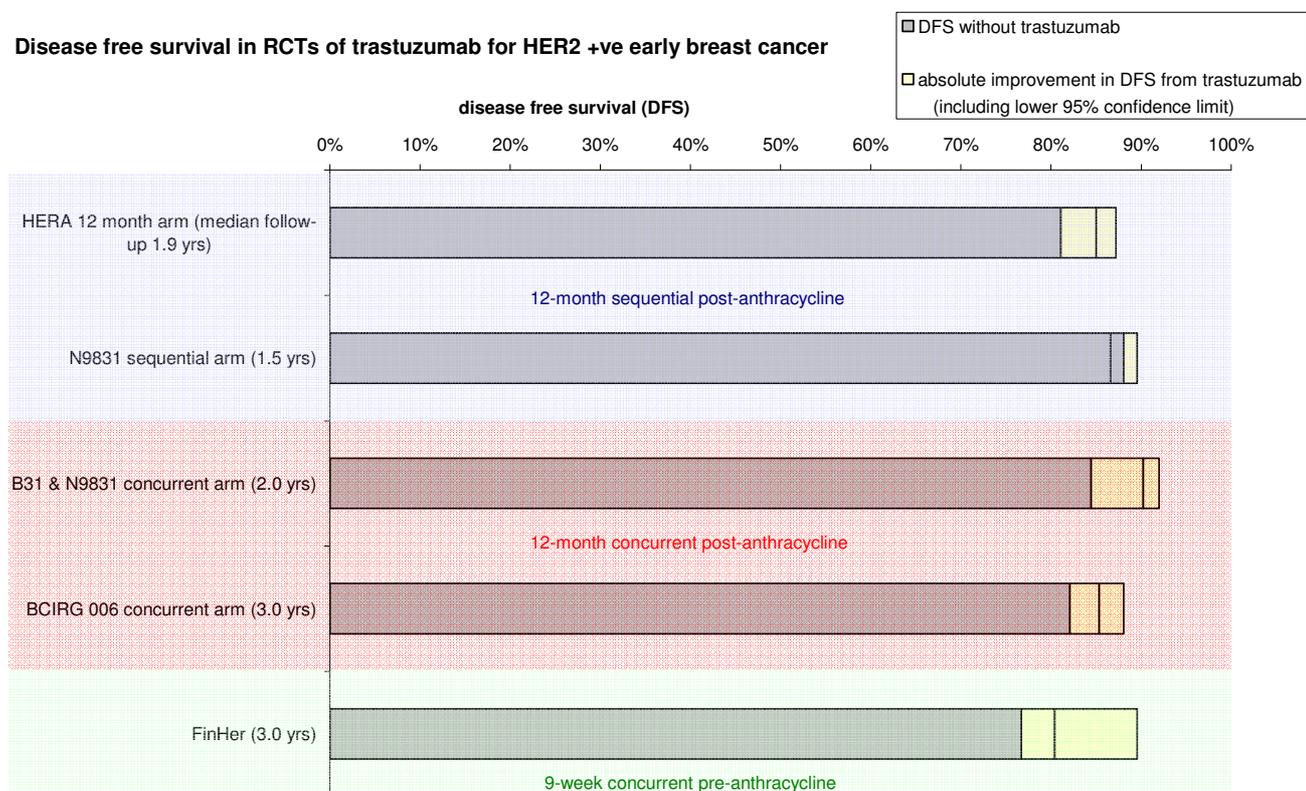


Figure 2. DFS in adjuvant trastuzumab trials in HER2-positive early breast cancer for untreated and treated groups, including minimum confident improvements (PHARMAC analysis)



Altogether, the results to date from the RCTs indicate that adjuvant trastuzumab confers a benefit in DFS and overall survival compared to standard chemotherapy, reducing both disease recurrence and overall deaths by 5.6% and 2.5% respectively at 2.2 years median follow-up (mf/u) compared with standard chemotherapy alone—a relative reduction of $\sim 1/3^{\text{rd}}$ compared with standard chemotherapy alone. All RCTs showed statistically significant DFS gains (except N9831 sequential arm, Arm B), with significant overall survival gains demonstrated in the joint B31/N9831 analysis (published as the Romond paper¹⁰), BCIRG 006 and HERA trials. Further details of the study results are provided in [Appendix 4](#).

However, there are disparities in trastuzumab treatment efficacy between the studies, i.e. differences in the HRs for DFS and overall survival between studies and regimens, and differences in the ranges of the confidence limits for those HRs:

- trials vary fourfold in hazard ratios for DFS (0.42 FinHer vs. 0.87 sequential arm of trial N9831, i.e. 58% vs. 13% relative hazard reductions);
- trials vary threefold in ranges of confidence limits (precision) (HERA 95% CI 0.54-0.76 vs. FinHer 0.21-0.83);
- trials vary eightfold in DFS absolute improvements (N9831 sequential arm 1.5% at 1.5 years mf/u vs. FinHer 12.8% at 3 years mf/u); and

- trials vary 7% in minimum absolute improvements in DFS from trastuzumab treatment (-1.5% for N9831 sequential arm at 1.5 years mf/u vs. 5.8% for B31/N9831 concurrent arm at 2 years mf/u— derived from upper limit of the 95% confidence interval for calculated DFS relative risks).

Grouping together the results across the trials with similar treatment regimens, overall (pooled) results for DFS vary between:

- concurrent treatment pre-anthracycline HR 0.42 (0.21-0.83) with 12.8% absolute risk reduction (minimum 3.7%) at 3.0 years mf/u;
- concurrent treatment post-anthracycline HR 0.53 (0.46-0.62) with 6.9% (minimum 5.5%) at 2.4 years mf/u; and
- sequential treatment post-anthracycline HR 0.70 (0.61-0.81) with 6.1% (minimum 2.7%) at 1.8 years mf/u (see Appendix 4).

In addition, the trials have a number of methodological issues that may affect their validity. Results from all five trials reported to date have been preliminary (interim)—all continue to follow-up patients, and none have met their preset target event accruals for final analysis. It is difficult to assess the quality of two RCTs (B31 and N9831) because reporting has been limited to either a published joint analysis for B31 and the N9831 control and concurrent arms (Arms A and C) (Romond 2005¹⁰)—with little disaggregation into the separate studies¹¹ or description of key validity aspects of the separate studies—or a conference slideshow presentation for N9831.¹² Results for BCIRG 006 also have been limited to conference slideshow presentations.¹³ All trials are open-label in design (unblinded), and allocation concealment methodology is not reported adequately (except for FinHer)—where inadequate or unclear allocation concealment has been associated with 30-40% larger estimates of treatment effects¹³ Finally there is variable reporting of compliance, contamination and co-intervention between the studies. Further details on the quality of the trials are available in GATE¹⁴ appraisals undertaken by EPIQ at

http://www.health.auckland.ac.nz/population-health/epidemiology-biostats/epiq/critical_appraisal_library/Herceptin^{15**}

Importantly, the result for the N9831 sequential arm (Arm B)—no statistically significant benefit of 12 months sequential trastuzumab over standard chemotherapy, HR 0.87 (95% CI 0.67-1.13)—raises questions about the efficacy of 12-month sequential trastuzumab and its place as the perceived ‘standard of care’. Trials examining trastuzumab as concurrent therapy (i.e. trastuzumab in combination with a taxane for 9–10 weeks or 12 months) consistently report better results in terms of DFS than sequential trastuzumab. The results of the FinHer trial to date appear to be comparable to those of the longer treatment regimens, although statistically significant overall survival gains have not been demonstrated to date (see [Appendix 4](#)).

Overall, the information available to date from all the clinical trials examining the use of trastuzumab for HER2-positive early breast cancer indicates that the optimal treatment schedule and duration of treatment for trastuzumab has not yet been determined. Appendix 4 describes this in depth. PTAC has reiterated that there is still uncertainty about the best way to administer trastuzumab in terms of optimal treatment duration, dose and schedule (sequential to, or concurrent with,

chemotherapy, before or after anthracyclines); minimising cardiovascular toxicity; and long-term clinical outcomes (fully minuted in [Appendix 5](#)).

PHARMAC and its decision-making processes

The Pharmaceutical Management Agency (PHARMAC) is the government agency that, under the New Zealand Public Health and Disability Act 2000, is responsible for securing the best health outcomes reasonably achievable from medicines within the funding provided (the allocated pharmaceutical budget). PHARMAC applies nine decision criteria when making pharmaceutical funding decisions (http://www.pharmac.govt.nz/who_are_pharmac.asp), has a fixed budget, and integrates clinical and economic assessment to help determine the next best use of this funding.

PHARMAC's role is to allocate taxpayer funds efficiently and ensure medicines are assessed comparably to result in fair funding decisions. Cost-effectiveness and budgetary impact (determining the relative value for money of a proposal in order to achieve best health gains from the budget available) are two of PHARMAC's nine decision criteria (http://www.pharmac.govt.nz/who_are_pharmac.asp). The way that PHARMAC has considered funding of the 9-week option for trastuzumab is no different to any other targeting means that PHARMAC uses to get the best health gains for a given medicine and ensure that other patient groups are not denied other treatments.

PHARMAC relies on objective advice from its clinical advisory body, the Pharmacology and Therapeutics Advisory Committee (PTAC) (<http://www.pharmac.govt.nz/ptac.asp>), on pharmaceutical agents and their benefits (section 50(1)(a) New Zealand Public Health and Disability Act 2000). Full minutes of relevant discussion about trastuzumab at the February, May, August and November 2006 and February 2007 meetings of PTAC are attached as [Appendix 5](#).

PHARMAC has an established consultation process for proposed changes to the Pharmaceutical Schedule. PHARMAC consults (and is required to consult) with sections of the public that, in PHARMAC's view, may be affected by decisions on those matters (including relevant clinical and patient groups)^{16,17} to ensure it has all necessary information before making a decision. PHARMAC consulted with interested parties on whether or not to fund the 9-week concurrent trastuzumab regimen (<http://www.pharmac.govt.nz/pdf/200307>) over a 3 week period during March/April 2007.

Nine-week trastuzumab regimen concurrent with docetaxel will be funded from 1 July 2007

Following consultation, PHARMAC recently announced funding for trastuzumab for HER2-positive early breast cancer when administered for 9 weeks concurrently with taxane chemotherapy. Because in the FinHer¹⁴ regimen docetaxel was the taxane of choice, PHARMAC has also approved funding for docetaxel for early breast cancer when given concurrently with trastuzumab; paclitaxel is already funded for node positive early breast cancer.

The 9-week concurrent regimen is considered by PHARMAC to be clinically effective and cost effective in terms of improving DFS, and affordable for DHBs in

terms of drug and resource costs. PTAC considered that the information on short term trastuzumab treatment from the FinHer and ECOG E2198¹⁸ trials suggested that comparable health gains, and possibly less cardiac toxicity, could be achieved with a shorter trastuzumab treatment regimen compared with 12 month treatment regimens. The Committee also considered that the FinHer results cast doubt over the optimal duration/timing for administration of trastuzumab; and that numbers of patients treated were not insignificant and the data were valuable. Having taken into account the views of its Cancer Treatments subcommittee (CaTSoP),^{††} PTAC recommended the 9-week regimen be funded with a high priority (fully minuted in Appendix 5).

The shorter duration concurrent regimen for adjuvant trastuzumab in the FinHer study¹⁴ was based on the concept of trastuzumab acting synergistically when given concurrently with taxane chemotherapy,¹⁹ as suggested by data from the use of this combination in the metastatic disease setting.²⁰ Subsequently, this hypothesis has also been supported by the trial N9831 comparison of sequential vs. concurrent administration of trastuzumab.¹² In theory, this short duration regimen may also be safer for patients in terms of cardiotoxicity risks, since trastuzumab is administered at a low overall dose and prior to cardiotoxic anthracycline chemotherapy^{‡‡}—administration of trastuzumab in combination with taxane chemotherapy following completion of anthracycline chemotherapy is associated with higher risks of cardiac toxicity than other treatment regimens.

The efficacy results (DFS in the HER2-positive groups treated with trastuzumab compared with no trastuzumab) of the FinHer trial demonstrate that administration of 9 weeks of trastuzumab concurrent with chemotherapy is effective in the treatment of HER2-positive early breast cancer (HR 0.42 (95% CI 0.21-0.83), absolute benefit 13.5% at 3 years mf/up), and PTAC considered these health gains comparable to the HERA trial results.

The evidence to support the 9-week concurrent regimen is sufficient in itself to justify funding. In short, advantages with the regimen are:

1. the 9-week concurrent regimen as examined by the FinHer trial gives statistically significant comparable results in terms of DFS to longer duration treatments (FinHer HR for DFS 0.42 (0.21-0.83))^{§§};
2. an estimated 15-20% more patients will be able to be treated by the 9-week concurrent regimen—because with the 9-week concurrent regimen patients are not exposed to their cardiotoxic anthracycline chemotherapy before initiating trastuzumab treatment^{***};
3. PHARMAC's cost-effectiveness analysis²¹ (available at <http://www.pharmac.govt.nz/pdf/030307c.pdf>) indicates that the 9-week concurrent regimen is, under fairly conservative assumptions with respect to the extent and duration of trastuzumab benefits, relatively cost-effective (\$14,500-\$16,500 per QALY). Trastuzumab in this setting is therefore considered to be as, or more, cost-effective than many other medicines PHARMAC has funded or is considering funding. Further, the 9-week concurrent treatment regimen is likely to be at least four times more cost-effective than the 12-month sequential regimen (50 QALYs per million spent for the 9-week regimen, 12.5 QALYs per million spent for the 12-month);

4. the shorter timeframe and fewer infusions will be easier for DHBs to deliver, and will have fewer impacts on DHBs' continuation of existing services (including reduced resources required to monitor cardiac function and provision of infusion services) than the 12-month sequential regimen; and
5. the 9-week concurrent regimen may be less cardiotoxic than long duration regimens, although this requires further data for confirmation.†††

Patients may also benefit from the convenience of the shorter timeframe and fewer infusions.

Some parties have questioned the reliability and validity of the 9-week concurrent trastuzumab regimen—because of the small sample size; use of vinorelbine (not docetaxel) in half of the patients; statistically non-significant results for overall survival at this time (HR 0.41(0.16-1.08)); and the evidence for short duration treatment being limited to this one study. These issues are canvassed in [Appendix 4](#), but it is noted here that:

- the large effect on DFS with FinHer's shorter duration concurrent treatment regimen ensured statistical significance despite small patient numbers (and 'many treatments are funded with a lesser degree of certainty'²⁷);
- the hazard ratio for DFS in FinHer is similar to that for the combined data from trials of the 12-month sequential regimens (HERA and Arm B of N9831) across all ranges of confidence, suggesting results little different for FinHer despite smaller numbers—the minimum extent that disease recurrence can confidently be expected to reduce in FinHer was 17% (from the upper CI for HR of 0.83, above), compared with 19% for 12-month sequential treatment overall (HR 0.70 (0.61-0.81)‡‡‡);
- informal post-hoc subgroup analysis of patients treated with docetaxel and trastuzumab (compared with docetaxel alone) reveals persisting statistical significance for the combination of trastuzumab and docetaxel, despite a halving of patient numbers;
- overall survival may emerge to become statistically significant (a strong trend in data published to date) once the 5 year median follow-up data for FinHer become available, expected this year; and
- the concept of shorter duration treatment is supported by the unpublished results of a pilot study, ECOG E2198,¹⁸ which compared 12-month and 10 week trastuzumab regimens given concurrently with paclitaxel, where the regimens have shown similar outcomes at 5 years follow-up.

PTAC's view was that the number of patients treated in the FinHer study was not insignificant and that the data from this trial were valuable (fully minuted in Appendix 5).

Practical aspects of the 9-week concurrent trastuzumab regimen

Details of how the subsidy rules will be amended in the Pharmaceutical Schedule can be found on the PHARMAC website at <http://www.pharmac.govt.nz/pdf/030307b.pdf>

The funded 9-week concurrent treatment regimen is not covered by the current New Zealand Datasheet for trastuzumab. Trastuzumab has provisional consent in New Zealand for HER2-positive early breast cancer when administered as sequential treatment (i.e. ‘... following surgery and completion of adjuvant chemotherapy’), based on the 12 month data from the HERA trial.⁷ Therefore, prescribers of the funded regimen must be aware of, and comply with, the provisions of section 25 of the Medicines Act 1981.^{22,23} §§§

Of note, the Australian indication for trastuzumab is for ‘in association with chemotherapy’ and allows for 12 months sequential, 12 months concurrent or 9 weeks concurrent treatment regimens to be used.²⁴ The Australian Product Information dosing section states that the optimal dosage regimen and treatment duration have not been defined, and that favourable risk/benefit ratios have been demonstrated with the regimens of the HERA trial, B31/N9831 trials and the FinHer trial.

Twelve-month sequential treatment is not presently a funding option

The 12-month sequential regimen (as per HERA⁷ and the current NZ datasheet⁶) has not been approved for funding by PHARMAC and DHBs for reasons relating to the uncertainty surrounding long term clinical benefits and risks^{21,25,26} the high budgetary impact, effects on DHB services provision, and its associated relatively high cost per quality adjusted life year (QALY)**** (i.e. the proposal was relatively poor value for money compared with other pharmaceutical funding options). In August 2006 PTAC recommended that 12-month sequential treatment with trastuzumab be declined, for similar reasons (fully minuted in Appendix 5).

In short, the 12-month sequential regimen does not provide the level of, and certainty about, health benefits that PHARMAC would expect to get from spending \$25 million per annum compared with other investment options.^{8,21} ††††

To date no new information has emerged to suggest that funding the 12-month sequential regimen is a viable option for PHARMAC or DHBs. In fact the already significant questions over the extent that sequential treatment prevents recurrence have only increased:

- In particular, the disease free survival gain in the HERA trial at 2 years’ median follow-up was less than that reported at the 12 month interim follow-up (the HERA DFS 12-month mf/u hazard ratio was 0.54 (95% CI 0.43-0.67)⁷; 2-year mf/u HR 0.64 (0.54-0.76)⁹)—a reduction that was statistically significant on testing for interaction by time (p=0.02).‡‡‡‡ This translates into an 8.3% absolute difference in DFS at the 12-month mf/u, reducing to 6.1% at 23-months’ mf/u—leading to doubt around the durability of efficacy of this regimen.²⁷ (see [Appendix 4](#)).
- Furthermore, there are concerns raised by the unpublished²⁸ results of the unplanned interim analysis of the sequential treatment arm of the N9831 trial.¹² These results indicated, despite large numbers in this part of the study (n=1964 compared in the sequential and comparator arms), no statistically significant benefit for sequential trastuzumab over standard chemotherapy (HR 0.87 (0.67-1.13)¹² (also [Appendix 4](#)). The median effect on DFS in the sequential arm of N9831 was comparatively small (the 0.87 HR, i.e. a 13% relative hazard reduction).

In addition, other questions over the long-term impact of demonstrable cardiac toxicity still remain (also Appendix 4). The impact of possible long-term cardiac effects should not be disregarded when it is likely that 70% or more of women with HER2-positive early breast cancer will still be alive at 10 years with standard adjuvant chemotherapy regimens without trastuzumab (see [Appendix 1](#)).

It has been suggested that the apparent waning of efficacy in HERA is due to cross-over contamination, where patients in the placebo-arm were offered trastuzumab treatment, in a non-randomised fashion, once the 12-month DFS results emerged. However, in the 23-months' median follow-up publication, Smith et al.⁹ reported that results from a censored analysis (where cross-over patient data were removed) (DFS HR 0.63) were much the same as those from the intention-to-treat analysis (ITTA; DFS HR 0.64). Therefore, this waning in efficacy cannot be explained simply by cross-over contamination alone. Importantly, this cross-over has limited the ability of this study to examine longer-term outcomes for 12 months' sequential trastuzumab compared to standard chemotherapy, because the standard chemotherapy arm has largely been lost, possibly to a point where longer-term comparison questions from this study can never be resolved.

Hence, the now apparent lack of significant benefit in the unpublished results from part of trial N9831^{10,12} and the reduced effect after 23 months' median follow-up from HERA^{7,9} means that PHARMAC's original estimate of the cost-effectiveness of the 12 month sequential regimen may have been overly optimistic (base case NZ\$70-80,000 per QALY).²¹ A formal update of the PHARMAC cost utility analysis of the 12-month sequential regimen²¹—including the recently published overall survival data from the HERA 23 month median follow up⁹—would be unlikely to show trastuzumab treatment to be any more cost-effective than suggested by the original analysis, as the majority of changes would disfavour trastuzumab. Therefore, PHARMAC has not formally updated the original analysis of the 12 month sequential trastuzumab regimen. Further details are available on the PHARMAC website at <http://www.pharmac.govt.nz/pdf/030307e.pdf> (an appendix to the PHARMAC technology assessment report for trastuzumab²¹).

Further publications arising from these two studies, including the third arm of HERA where patients were given 2 years of trastuzumab and longer term follow-up outcomes, are awaited with interest.^{28,29}

Trastuzumab around the world

A number of other countries have approved funding for trastuzumab, using a 12-month treatment regimen. In most of these countries, assessment of funding a medicine is limited to the licensed indication which is largely dictated by data provided by, and supported by, the supplier. The licensed indications for trastuzumab treatment regimens vary throughout the world. In the United States, where trastuzumab is marketed by Genentech, trastuzumab is approved for use in combination with taxane chemotherapy (concurrent treatment).³⁰ In Europe, however, it is registered for 12 months treatment after completion of all chemotherapy (sequential treatment). Alternatively, in Australia there are a number of options for using trastuzumab including long and short duration, and using it concurrently with, or sequentially to, taxane chemotherapy.²⁴

Funding for cancer treatments in New Zealand takes place within DHBs' budgets, so choices have to be made about how to allocate spending most efficiently.³¹ Most other countries, including the United Kingdom and Australia, do not appear to have such direct budgetary constraints and associated prioritisation processes. The fact that other OECD countries fund 12 months Herceptin is not in itself a reason for New Zealand to follow-suit; funding decisions need to be made within countries' own decision-making frameworks, priorities and healthcare environments. Different countries have differing funding mechanisms and levels of governance and process, from 'no assessment required' (with associated opaque trade-offs) to more comprehensive decision-making and explicit prioritisation systems. PHARMAC relies on its established process and Decision Criteria when making funding decisions.

In the UK, the National Institute for Health and Clinical Excellence (NICE) makes its recommendations independent of budgetary considerations.³² However, debate in the UK is now suggesting that funding of 12 months trastuzumab is forcing the National Health Service to cut the funding from other health services, underlining the need to make careful choices.³³ Trastuzumab underwent inaugural assessment under NICE's single technology appraisal process, where (contrary to standard appraisals) evidence is provided solely by the supplier³⁴ (where for instance the FinHer data and the unpublished N9831 sequential data were not provided²⁶). One commentary has stated that NICE might never have deemed the 12-month sequential (HERA) schedule to be cost effective had FinHer been assessed as a comparator.²⁷

Similarly, it is not readily apparent from information to date whether other countries have carefully weighed up the 9-week concurrent versus 12-month trade-off. This is not to judge those decisions—each country will decide what is right for them—but meaningful comparison of New Zealand's approach to other countries needs to know whether the trade-off has been explicitly considered. At present, no such meaningful comparison seems possible.

PTAC's view on trastuzumab for early breast cancer has differed from those of clinical committees in other countries. There has been a strong emphasis by PTAC and PHARMAC on the uncertainty with the current clinical evidence²⁷ and corresponding impact on future outcomes, given the cost. PTAC also took into account both the 12-month regimen's unfavourable cost effectiveness compared to other funded medicines or medicines awaiting funding, and the practical implications for DHBs of administering this medicine under a 12-month regimen. In several countries, commitments were made to fund trastuzumab for HER2-positive early breast cancer prior to its evaluation by the European Agency for the Evaluation of Medicinal Products (EMA) and assessment by the relevant technology appraisal agencies.³⁵

This is not the first time New Zealand has chosen a different path to other countries. For instance PHARMAC declined to fund COX-2 inhibitors in 2004 because of concerns over both safety and cost—a stance better understood with time.³⁶

Conclusion and final comments

This paper describes PHARMAC's clinical and economic considerations for trastuzumab for HER2-positive early breast cancer. Like all funding decisions, a wide range of factors are relevant and important to inform decision-making. While some

may argue that clinical effectiveness *alone* is what is important, the reality of funding decisions in a cost constrained environment (where Health dollars are not infinite) is that clinical effectiveness must be considered alongside other relevant decision factors. Such factors include economic and practical considerations, and comparison with other health opportunities—the very basis for PHARMAC’s nine Decision Criteria. Hence clinical and funding imperatives are inextricable to PHARMAC’s decision making.

A comparison of the 12-month sequential and the 9-week concurrent trastuzumab regimens, in terms of both opportunity cost (costs of trastuzumab and impacts on DHB services related to administration) and cost-effectiveness, is included in [Appendix 6](#).

With the funding of the 9-week concurrent regimen, DHBs and PHARMAC have sought a practical and workable solution to enable subsidised access to an effective trastuzumab treatment for HER2-positive early breast cancer patients. DHBs support the funding of 9-week trastuzumab, and have stated the \$6 million per annum overall cost (which includes drug cost and administration costs) of providing this regimen to be viable.

There is need for women with HER2-positive early breast cancer to be able to fully and readily access this fully funded option for trastuzumab. However, simply listing trastuzumab on the Pharmaceutical Schedule in this setting will not necessarily reduce the regional variations in testing for HER2-positivity that already occur, nor improve ethnic disparities—where current health inequalities have existed³⁷ before and regardless of the availability of trastuzumab ([Appendix 2](#)). Health need, the availability of other treatments and the Government’s priorities for health funding (which include cancer) are also included in PHARMAC’s decision criteria; as with breast cancer, there are other areas of high need that also need to be considered when assessing competing funding choices (see [Appendix 1](#)).

PTAC considers that more clinical research is needed to determine if long duration concurrent treatment (12 months) is more efficacious than short duration concurrent treatment (9 weeks), and has recommended that a comparative study should be performed ([Appendix 5](#)). PHARMAC remains open to the possibility of funding longer regimens of trastuzumab, if data indicate that funding would not result in unacceptable opportunity costs. To this end, PHARMAC has already committed funding for international efforts (the SOLD trial) to resolve the question of optimal duration,³⁸ given the lack of direct head-to-head comparative evidence for the superiority of either 9-week or 12-month regimens.

Competing interests: None.

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Endnotes:

* In July 2006, PHARMAC decided not to fund the 12-month sequential regimen at that time. There is uncertainty about the long-term treatment benefits in relation to the very high cost and impact on hospital services. This uncertainty has implications for future treatments measured against (or added to) standard-of-care regimens that include 12-months of sequential trastuzumab in the clinical trial setting.

PHARMAC was asked by the supplier to make a decision on funding 12-month trastuzumab predominantly on the basis of the results of the HERA trial's interim report of the effects of 1-year's sequential treatment after 12 months median follow-up (Piccart-Gebhart et al NEJM 2005⁷). PTAC raised a concern over the durability of response and the long-term balance of safety and efficacy. PHARMAC had concerns over the uncertainty from a cost-effectiveness point of view for such a relatively large investment in a pharmaceutical (around \$25m per annum out of a total cancer spend of about \$50m per annum), in relation to PHARMAC's legal responsibility to 'secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided' (s47 NZPHD Act 2000). According to PHARMAC's analysis, in order for 12-month trastuzumab to be considered cost-effective in comparison with other pharmaceuticals being considered for funding, the response would have to be durable and become progressively better over time. This finding was consistent with the result of other international analyses.^{26 8}

† Currently docetaxel and paclitaxel are funded and available through DHB hospitals for metastatic breast cancer (Stage IV), and paclitaxel for node-positive early breast cancer.

‡ A sixth study, ECOG E2198 (Sledge et al. SABCs 2006¹⁸), 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; however this study has not reported outcomes against standard treatment.

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

** PHARMAC commissioned Dr. Susan Wells, Senior Lecturer in Clinical Epidemiology at EPIQ (Effective Practice, Informatics & Quality Improvement www.epiq.co.nz), University of Auckland to further critically appraise the five relevant clinical trials (HERA, B31, N9831, BCIRG006, and FinHer) using the full Graphic Appraisal Tool for Epidemiology (GATE) framework (<http://ebm.bmj.com/cgi/content/full/11/2/35>), in order to summarise and independently assess the strength and quality of all the available relevant RCTs.

Dr Wells obtained both specialist clinical epidemiological peer review and specialist oncologist content review of each of the GATE appraisals. The analysis was restricted to critically appraising the five individual RCTs as published or otherwise reported; it was not intended to integrate the epidemiological evidence with patient preferences, policy issues or clinical considerations, nor provide a meta-analysis or systematic review or other formal policy advice.

†† The CaTSOP recommended that, in the absence of availability of funding for 12-months treatment, 9-week treatment would be reasonable and gave this recommendation a high priority. The subcommittee did however wish to emphasise that this recommendation was strongly based on financial considerations, since the subcommittee had more confidence in the 12-month treatment results.

‡‡ "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 than trastuzumab given as a single agent.” (Joensuu – SOLD protocol)

§§ The efficacy results of the FinHer trial suggest that concomitant administration of trastuzumab with docetaxel is effective in the treatment of HER2-positive early breast cancer. In the FinHer study 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 follow-up time of 3 years these treatments were not associated with detectable cardiac toxicity. The data suggest that the combination of docetaxel plus 9-week concomitant trastuzumab is effective and well tolerated in the treatment of HER2-positive breast cancer.

*** More patients would be eligible for trastuzumab under the FinHer regimen than the 12 month HERA sequential regimen or Romond (B31, N9831 Arm C) concurrent regimen, because patients receive their cardiotoxic chemotherapy (anthracycline) after trastuzumab in the 9-week regimen, therefore, more patients would be expected to meet the cardiac inclusion criteria required for trastuzumab treatment. Using the methods and base assumptions used in the KCE 2006 report (pages 51, 72), applying excess rates of LVEF decline (sourced from Romond 2005, etc.–see KCE 2006⁸) to age-specific New Zealand HER2+ve breast cancer registration data (Cancer Register breast cancer registrations August 2001-December 2005, obtained from NZHIS) means potentially 18% more patients would be able to receive trastuzumab treatment with the 9-week concurrent regimen as per FinHer compared with 12-month sequential or concurrent treatment regimens.

year 2005 breast cancer registrations	NZ HER2
all	2389
(early breast cancer)	2274
HER2+ve	385
% HER2+ve / all CAB	16%
aged <80, HER2 +ve CAB	364
HER2+ve CAB, aged <80 / all ages	95%
(all CAB, aged <80)	2095
aged <80, % HER2 +ve / all CAB	17%
year 2005 HER2+ve CAB aged <80	
(figure used in DHB CEO paper mid-2006)	314
excl pre-existing CVD	347
all (incl pre-existing CVD)	364
w/o LVEF <50%, pre-AC	355
w/o LVEF <50%, post-AC	301
extra pts without LVEF, no pre-AC	55
% extra pts without LVEF, no pre-AC	18%

††† The low cardiotoxicity observed in FinHer could also be explained by the relatively low cumulative total dose of 180 mg/m² epirubicin while the maximum tolerated cumulative dose of epirubicin is around 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 compared with doxorubicin. The KCE report⁸ states that in terms of cardiotoxicity that no conclusions however can be drawn on the relative importance of the trastuzumab anthracycline treatment order, on the duration of trastuzumab administration, nor on the type of anthracycline and its dose. Multiple variables differ between the pre- and post-anthracycline regimens studied.

‡‡‡ The minimum extent that disease recurrence can confidently be expected to reduce in FinHer was 17% ((HR 0.42 (95% CI 0.21-**0.83**), hence minimum relative hazard reduction (RHR) = 1-0.83 = 0.17). This compares with a 19% minimum extent that disease recurrence can confidently be expected to reduce with 12-month sequential treatment (combined HERA 23-month median follow-up and N9831 Arm B data overall HR 0.70 (0.61-**0.81**), hence minimum RHR = 1-0.81 = 0.19)

§§§ Section 25 of the Medicines Act 1981 allows the practitioner to "procure the sale or supply of any medicine" for a particular patient in his or her care. "Any medicine" includes approved and unapproved medicines. The Act puts no restriction on the use of a medicine, even in a situation in which it is contraindicated. However, whether the practitioner uses approved or unapproved medicines, they must provide care of an adequate professional and ethical standard. Clinicians need to obtain informed consent from their patients for such 'off-indication' use.

Section 25 prescribing is not unusual in oncology or other areas of medicine, with rates stated to be up to 40% in adults and up to 90% in paediatric patients.²³ Routine off-label use can be justified if there is high-quality evidence supporting efficacy or effectiveness.²³ There are already a number of unapproved indications present in the Pharmaceutical Schedule listings for cancer treatments.

The evidence required to make a funding decision is not necessarily the same as that required to instigate a Datasheet change. In the context of a funding decision, PHARMAC considers that the level of evidence for 9-week concurrent trastuzumab, when combined with other decision criteria, does justify giving clinicians and patients the choice to access a funded treatment under Section 25. There would be no compulsion on oncologists or their patients to exercise that choice. The evidence required for a change to the Datasheet may need to be different, since the Datasheet dictates the supplier and Medsafe liabilities with respect to a product.

With any product there is a continuum of data, ranging from weak data in some settings, to statistically strong and repeatable data in other settings. Decisions regarding different applications of this continuum of data are based on different 'hurdles' for levels of evidence. For example Section 29 and Section 25 of the Medicines Act 1981 specifically aim to permit clinicians to use their discretion where they consider that the available evidence justifies prescribing a drug for a particular patient outside the Medsafe approved indication. In some cases it appears that evidence will simply not have been made available to the regulator to enable Datasheet changes.

**** A QALY (quality-adjusted life year) is a standard economic measure that considers how treatment affects patient quality of life and quantity of life; QALYs combine the effects of changes in the length and quality of life that result from treatment. The difference in net costs and QALYs between treatments informs the relative cost-effectiveness of an intervention, with a lower cost per QALY being more cost-effective. For further details, see PHARMAC's Prescription for Pharmacoeconomic Analysis at http://www.pharmac.govt.nz/pharmo_economic.asp

†††† PHARMAC's indicative cost-utility analysis for 12-month trastuzumab suggested relatively poor quality adjusted survival benefits and nominal savings to DHBs, at \$70-80,000/QALY base case. This analysis showed a large range of plausible outcomes, largely due to the uncertainty surrounding duration of benefit and untreated disease progression. However, none of the plausible outcomes gave sufficient confidence that 12 months of trastuzumab treatment would be a cost-effective use of health funds compared with other investments.

‡‡‡‡ PHARMAC analysis of the two HERA publications (Piccart-Gebhart 2005, Smith 2007).

The 23-month median HERA f/u (Smith 2007) comprises cumulative hazards over the entire 23 months, with 218+321=539 first disease recurrence events—in turn comprising events and hazards reported as accruing by the first 12 months median f/u (Piccart-Gebhart) (127+220=347 events) and then the complement of events for the remaining time period (539-347=192), i.e. events occurring in the time since the first analysis. Analysis therefore involves subtracting events recorded as accruing in the first time period (12 months median follow-up) from the cumulative events recorded as accruing over the whole time period analysed to date (23 month median follow-up). This derives numbers of events occurring in the time since the first analysis, in order to calculate period-specific rates and relative risks. In turn this allows testing for statistical interaction (comparing the two time periods) using standard binomial methods (Matthews & Altman BMJ 1996 <http://www.bmj.com/cgi/content/full/313/7061/862>, Altman & Bland BMJ 2003 <http://www.bmj.com/cgi/content/full/326/7382/219>). See [Appendix 4](#) for further details.

§§§§ The Synergy or Long Duration (SOLD) study will assess the incremental efficacy and risks of adding an extended period of sequential trastuzumab to a short course of concurrent therapy (prior to anthracyclines) in HER2-positive early breast cancer. The trial, planned to enrol 3,000 patients internationally and follow them for at least 5 years, will compare 9 weeks' trastuzumab, concurrent with chemotherapy (the FinHer regimen), compared with an additional 42 weeks of trastuzumab.

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