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PHARMAC responds on Herceptin assumptions and decisions

We welcome the comments of Drs Richard Isaacs, Chris Frampton, and Marion Kuper-Hommel about the funding in New Zealand of adjuvant trastuzumab (Herceptin) for HER2-positive early breast cancer.[1] PHARMAC considers that, in terms of its decision criteria, the available evidence for 9-weeks therapy, given concurrently with taxanes, offers sufficient clinical benefits to justify its funding, relative to other choices.

PHARMAC has weighed up the available evidence, together with the wider and longer-term health care costs, in a logical, systematic, and transparent[2,3] fashion. This has included accounting for the results of the larger trials, fully and in their entirety, with aspects of study quality beyond size[4] and missing data.[5]

FinHer[6] was a good trial giving adequate information to inform a concurrent 9-week funding decision. The evidence for longer duration regimens from the larger trials is hampered by good evidence of significant and appreciable waning[7] (suggesting poor durability[2]) and the non-publication of ostensibly good and highly relevant trial data from nearly 1000 participants.[2,5] These missing data may confirm that sequential 12-month treatment is much less efficacious than concurrent and than previously thought, as was seen in their interim presentation,[5] and either way the data are important and need to be published.

Responses to the correspondents' specific points are in Table 1 below. Much of their arguments were already discussed in detail in the appendices (see links below) to the PHARMAC article itself, which *inter alia* described in some depth the survival with HER2-positive early breast cancer, epidemiology, and ethnic/regional disparities, and clinical effectiveness including publication bias.

The emerging evidence[2] will feed into debates internationally about the optimal use of trastuzumab. The optimal 'standard of care' is uncertain. Uncertainty around sequencing and duration is a real issue and urgently needs to be addressed. There needs to be full publication of all trial data around sequential treatment, formal analysis of its durability, and proper trial evidence to confirm optimal duration of treatment.

PHARMAC is supporting the SOLD trial internationally to help resolve the duration question. Whilst awaiting these comparative data, PHARMAC has taken the proactive pragmatic approach of funding the concurrent 9-week regimen that is considered cost-effective[8]—rather than funding nothing, as currently the sequential 12-month regimen is not considered cost-effective[8] and is unjustifiable under PHARMAC's nine decision criteria.[9]

Once again, we appreciate the open debate of the issues in the peer-reviewed setting,[10] as discussion of all of the evidence and its analysis is critical to understanding the quality of PHARMAC's decisions.

Conflict of interest: PHARMAC is currently the subject of a Judicial Review of its decisions to fund a concurrent 9-week regimen of trastuzumab as adjunctive treatment of HER2-positive early breast cancer and not to fund a sequential 12-month regimen at this stage.

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Table 1. Specific concerns and PHARMAC responses

Topic	PHARMAC response
Large patient numbers in trials of longer duration treatment, vs. two small studies for shorter duration	As covered in PHARMAC's article, major doubts persist as to optimal treatment sequencing and duration. It is incorrect to combine all of the 12-month studies together, especially given head-to-head RCT evidence of significant differences in efficacy and side effects according to sequence[5]; given such logic, it would be equally appropriate to compare all concurrent treatments, including the FinHer regimen[6], against sequential regimens.[5,7] Trials of the 12-month sequential regimen, the regimen for which funding was sought, covered 5,365 patients, demonstrating a 30% relative reduction in disease events (HR 0.70, 95% CI 0.61-0.81). These patients comprised 3,401 women in the 12-month trastuzumab and standard care arms of HERA[7] and 1,964 women (2/3rds as many) in the 12-month sequential trastuzumab and standard care arms of trial NCCTG-N9831[5]—a comparison whose publication is still awaited.
FinHer's power and efficacy	Our stance on the statistical power of the FinHer trial remains unchanged, described on pages 28-30 of Appendix 4 (http://www.nzma.org.nz/journal/120-1256/2593/Afour.pdf). This includes (but is not restricted to) FinHer's results being statistically significant *despite* its smaller size. As few as 145 patients would have been needed for the results to still be statistically significant. Large treatment effects—likely to be more clinically worthwhile—but with wider confidence intervals (greater imprecision) should not be ignored essentially because of less power. Such concerns are analogous to post-hoc power calculations—where in fact once results are available, a trial yields a treatment effect and confidence interval for the results, and the power of the trial is expressed in that confidence interval; hence 'power' is no longer a meaningful concern.[11] Although patently the results of FinHer are numerically less precise than those of HERA or the other large studies, the DFS results were statistically significant at the p=0.01 level, in other words the odds are 99 times out of 100 that improvement in DFS in FinHer would not be attributable to chance alone, and many treatments are funded with a lesser degree of certainty.[12] RCT data from 208 patients (TAnDEM) were sufficient for the EMEA to license the use of trastuzumab with aromatase inhibitors in metastatic disease.[13] Compared with sequential 12-month treatment (updated HERA data[7] and the sequential arm of trial N9831[5]), at the very worst—i.e. the minimum extent that disease recurrence can confidently be expected to reduce, using upper confidence limits for hazard ratios—the FinHer results were as effective as sequential regimens (17% and 19% minimum relative hazard reductions respectively), even with its smaller number of patients.

Table 1. Specific concerns and PHARMAC responses *(continued)*

Only 54 FinHer patients used trastuzumab and docetaxel	Interestingly, the 54 patients in FinHer using trastuzumab with docetaxel still showed significant improvements in disease free survival (DFS) compared with those using docetaxel alone, despite low numbers. Such comparison is duly caveated in Appendix 4; these caveats however extend to the correspondents' restricting analysis to docetaxel patients alone. Using the correspondents' logic would require restricting HERA data analysis interpretation to its 889 patients who received 'standard of care' anthracycline and taxanes, where DFS effects were reduced and not statistically significant (HR 0.80 (0.59-1.10)). We are not seriously advocating this post-hoc approach, but neither should the FinHer data be so separated.
Standard regimens in the trials Receipt of protocol chemotherapy in FinHer	Chemotherapy regimens in FinHer were no less standard than the regimens in other trials. A similar docetaxel regimen to FinHer was also used in BCIRG 006; the NSABP B31 and NCCTG N9831 trials (Romond 2005[14]) used paclitaxel. Other trials (the basis for continuing calls for longer duration treatment) had similar issues with patients not receiving full-dose or protocol-specified therapy. In the HERA trial chemotherapy was not specified, therefore there was large variation in the regimens and doses used, and only 26% of patient received taxanes and 6% received no anthracyclines at all; doses of docetaxel in HERA (11%) were not described.[7] The other studies have yet to describe rates of patients reducing their docetaxel doses (or indeed other chemotherapy drugs) as a result of adverse effects.
Methodological flaws in longer duration trials, and the balance of the FinHer trial arms	The methodological and reporting issues with the studies are more than minor (http://www.health.auckland.ac.nz/population-health/epidemiology-biostats/epiq/critical_appraisal_library/Herceptin).[4] FinHer was a properly randomised trial with adequate reporting and concealment of allocation. Randomisation is designed to eliminate confounding bias, both known and unknown; randomisation balances out groups, including unknown factors, and groups will be by definition balanced, occurring as a matter of course. The baseline characteristics/prognostic indicators of the treatment groups were generally well balanced, and less favourable axillary nodal metastases and progesterone-negative tumours tended to be more frequent in the trastuzumab group. Such factors tend to cancel each other out—the whole point of appropriate randomisation. The impact on the overall outcome is therefore considered to be minimal. FinHer was the only trial of the five that adequately reported its methods for concealing allocation—where inadequate or unclear allocation concealment has been associated with 30-40% larger estimates of treatment effects,[11] conceivably overstating other regimens' effects.
Discussion of overall survival	In Appendix 4 (pages 30-31) we discussed in some detail the issues around overall survival for the short duration and long duration regimes. We invite wide readership of this material. FinHer's non-significant overall survival (OS) results to date, well-acknowledged, probably result from the combination of the small sample size and short follow-up at the time of analysis; significant improvements in OS may become evident in the final 5-year median follow-up analysis of FinHer expected later this year. This mirrors that of the sequential 12-month treatment, where the initial lack of overall survival benefit with the HERA study did not prevent widespread calls for its funding—via linkage to the significant OS results for concurrent regimens. Whilst HERA does now show significance in OS, there still remain serious questions about the efficacy and durability of sequential trastuzumab.

Table 1. Specific concerns and PHARMAC responses *(continued)*

ECOG-2198	Our article and Appendix 4 went to some pains to note that trial ECOG-E2198 (comparing shorter- with longer-duration trastuzumab regimens) was a pilot study and we excluded it from further analysis. It simply supports the concept of efficacy with shorter, concurrent, treatment.
HERA's waning of effect	The point with the waning of DFS benefit with longer-term follow-up with the HERA study[7] is that it questions how durable sequential treatment really is—where the implication has been, unquestioned, that short-term benefits will last. This brings doubt on the sequential 12-month regimen advocated, particularly when other important data have not been published and are therefore out of mind[5]—data that cast further doubt on the extent of the effectiveness of sequential 12-month treatment. This latter point needs to be acknowledged more widely. As noted in the article and in Appendix 4 (pages 16-17), contamination, being the cross-over of patients in HERA to the control arm, seemed to have little influence—the opportunity to cross-over occurred relatively late, and the DFS hazard ratios for both intention-to-treat and censored analyses were identical. This concordance of hazard ratios suggests a genuine waning of effect, not a crossover artefact as argued by the correspondents. By contrast, FinHer's central effects estimates were maintained at three years, similar to patterns seen with other concurrent regimens (http://www.nzma.org.nz/journal/120-1256/2593/Afour.pdf).
International view of the ethics of continuing studies when controls are without 12 months treatment	The correspondents' claimed international view on the ethics of control groups without 12 months trastuzumab is unreferenced and its universality needs to be verified. We also wonder whether any such an international view, if confirmed, will change, at least for sequential treatment, as other countries grapple with the implications of the non-publication to date of the NCCTG-N9831 Arm B (sequential) data.[5]
CaTSoP's role and recommendations	CaTSoP is one of 12 specialist subcommittees to PTAC (http://www.pharmac.govt.nz/sub_committee.asp), advising PTAC which in turn gives free and frank advice to PHARMAC (http://www.pharmac.govt.nz/ptac.asp). The subcommittee structure provides clinical evaluations in specialist areas; PTAC puts specific questions to subcommittees relating to actual clinical practice and real-world issues in their specialty areas. Subcommittees are subordinate to PTAC, providing information necessary for PTAC's work but that is insufficient in itself. CaTSoP itself in April 2006 gave the sequential 12-month treatment only a low/medium priority, highlighting problems such as resource constraints, opportunity costs, and long-term uncertainty. This recommendation was from oncologists for what had been heavily promoted as an exciting and important "wonder drug". Based on this advice from CaTSoP and its own assessment of other information, PTAC in August 2006 recommended the sequential 12-month sequential regimen be declined. So in October 2006, CaTSoP was being asked to consider concurrent 9 weeks in isolation, without recourse to sequential 12-month treatment. CaTSoP's minute for that meeting noted the following: 'At its 17 August 2006 meeting PTAC recommended that the application for the funding of trastuzumab as per the HERA protocol (12-months treatment) be declined and that the application be referred back to the Cancer Treatment Subcommittee of PTAC to consider the clinical appropriateness of any funding regimen consistent with the FinHer protocol (9-weeks treatment)'. CaTSoP could have said it was not clinically appropriate to fund concurrent 9 weeks, but did not. The subcommittee instead recommended that, in the absence of availability of funding for sequential 12 months treatment, concurrent 9-weeks treatment would be reasonable and gave this recommendation a high priority. However, CaTSoP noted, and wished to emphasise, that this recommendation was strongly based on financial considerations since the subcommittee had more confidence in the validity of the 12-month treatment results. See Appendix 1 (accessible at http://www.nzma.org.nz/journal/120-1260/2692/Aone.pdf) for a copy of the full minutes for CaTSoP's April and October 2006 meetings relevant to trastuzumab in early breast cancer.

Table 1. Specific concerns and PHARMAC responses *(continued)*

PHARMAC's budget	PHARMAC's role is to work with the DHBs and determine how to allocate the funding the DHBs are supplied between pharmaceutical spending and other spending. There are many competing options, and in this case the levels and certainty of health benefits with the 12-month regimen were modest compared with the magnitude of funding, resource implications and opportunity costs (http://www.pharmac.govt.nz/pdf/030307c.pdf) so that it did not amount to a good funding choice. Wider issues of funding and budget setting are currently undergoing review as part of the government's review of its Medicines Strategy (http://www.moh.govt.nz/moh.nsf/pagesmh/5633/$File/towards-newzealand-medicines-strategy-consult.doc).
Adoption of expensive new treatments	The quality of care is not an automatic given with the uptake of new therapies. The report cited by the correspondents (Jönsson & Wilking 2007), paid for by Roche[15,16], has been criticised on a number of grounds[15,17], including: • New and expensive cancer drugs might not be any more effective than therapies already in use. In terms of value-for-money, one reason a drug may not be recommended is that it isn't sufficiently better than other drugs already available to make it cost effective.[15] • Population-based, comparative survival studies have known limitations[18], and the ranking of countries according to survival with cancer may be flawed.[19] Reporting biases, which will understate cancer-ascribed mortality rates in some countries, result in other countries such as the UK (and NZ) having over-stated high comparative mortality rates. This is where not all countries are able to link into national mortality statistics and automatically be notified of cancer-related deaths.[15] • The report relates the availability of cancer drugs in 38 countries in Europe in 2000 with the 5-year survival of patients diagnosed in those countries during 1990-94, some 6-10 years earlier. For 12 of the 38 countries involved, no such survival data are said to actually exist.[20] • For most cancers, higher survival is considered to result from earlier diagnosis and a combination of expert surgery and/or radiotherapy, as well as from the use of cancer drugs.[16] 'Huge decreases' in cancer mortality in the UK have been considered to be largely due to a downturn in deaths caused by tobacco, and dramatically improved breast cancer survival rates, mostly attributed to the success of hormone therapies.[15]
Price and negotiation with suppliers	Negotiation with suppliers is a key feature of most PHARMAC funding decisions. While price is clearly important, PHARMAC is ultimately most interested in the *value* of funding decisions (population health gains, etc, not just the price). Decisions involve inseparable clinical and funding imperatives, and trastuzumab has been no different. While understanding suppliers' commercial drivers, PHARMAC is always, in effect through its negotiation and other purchasing strategies, scrutinising pricing policies by incentivising suppliers to offer attractive funding proposals. Some commentators have also argued that suppliers should be more accountable to the public about why some medicines are priced at the level they are. In this wider context, Richard Peto, for example has been quoted "Patient organisations may call for all effective treatment to be available for free, but if this was the case it would be exploited wholly by drug companies for corporate profit—they would double their prices overnight. The price rise in drugs has been unprecedented and is made more acceptable by reports like these. There is too much criticism of the NHS and not enough of these companies' pricing policies."[15]

Appendices to Metcalfe et al NZMJ 15 June 2007[2]:

- Appendix 1: HER2 positive breast cancer, its treatment and prognosis (including survival) http://www.nzma.org.nz/journal/120-1256/2593/Aone.pdf
- Appendix 2: Epidemiology of HER2 positive breast cancer in New Zealand, with ethnic/regional disparities http://www.nzma.org.nz/journal/120-1256/2593/Atwo.pdf
- Appendix 3: Table of trials http://www.nzma.org.nz/journal/120-1256/2593/Athree.pdf
- Appendix 4: Clinical effectiveness (including publication bias) http://www.nzma.org.nz/journal/120-1256/2593/Afour.pdf
- Appendix 5: Relevant PTAC minutes http://www.nzma.org.nz/journal/120-1256/2593/Afive.pdf
- Appendix 6: Comparisons between 12-month and 9-week regimens http://www.nzma.org.nz/journal/120-1256/2593/Asix.pdf

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