



PHARMAC's funding of 9 weeks Herceptin: many assumptions in a high-risk decision

Metcalf et al¹ recently presented in the *Journal* the reasoning behind PHARMAC's decision to fund 9 weeks of trastuzumab (Herceptin®) as adjuvant therapy for early stage HER2-positive breast cancer.

They state that 'the evidence for the 9 week concurrent regimen was sufficient to justify funding' and put this 9-week regimen forward as the standard of care for the treatment of women with early stage Her2 positive breast cancer in New Zealand. By contrast, regulatory authorities in 23 other OECD countries have instead accepted 12 months of therapy as standard treatment. We strongly maintain that there is currently insufficient evidence to be confident a shorter duration of therapy offers equivalent benefits.

The use of Herceptin as adjuvant therapy for HER2-positive breast cancer has been heralded as a major advance in breast cancer treatment. The benefits, as described by Metcalfe et al, are documented by four large international studies²⁻⁴ of adjuvant Herceptin which recruited >12,000 patients in studies of 12 months Herceptin treatment duration, while there have been two small trials looking at 9-10 weeks of therapy using a non-standard chemotherapy regimen.

One of the short duration trials,⁵ described by Metcalfe et al, was a cardiac safety study that was not designed and had too few patients to assess efficacy. Furthermore, of the 227 patients in this trial, only 157 were HER-2 positive on central review. Thus the only published short duration trial of treatment efficacy is FinHer,⁶ which enrolled 232 patients in total, with only 54 in the PHARMAC-mandated New Zealand treatment arm of Herceptin concurrent with docetaxel.

This study lacks the statistical power in its own right to be used as the sole justification for a standard of care, and PHARMAC's assessment of its significance relies heavily on the findings from 12 month studies and an implied, but far from proven, assumption that 9 weeks has equivalent efficacy.

The large 12-month duration studies have all shown not only statistically significant disease-free, but also overall survival benefits at a remarkably early stage. This pattern of benefit has now been maintained at 4 years follow-up in two of the large studies,² predicting persistent and potentially curative benefits—as seen with other adjuvant systemic therapy studies of tamoxifen and chemotherapy at 15 years follow-up.⁷

These findings emphasise the efficacy of Herceptin when given in a 12-month schedule. Critically, and most disappointingly, Metcalfe et al do not discuss the fact that all the published 12 month trials have shown statistically significant overall survival benefits, while the 9 week FinHer trial did not.

Overall survival benefits are still recognised as the 'gold standard' of oncological treatment efficacy. Put bluntly, New Zealand women are to be denied a treatment regimen which has been robustly shown to save lives and are instead to be offered one which has not.

Metcalf et al make much of the apparent waning of benefit with longer follow-up in the sequential HERA study,³ but the benefits remain large at 2 years median follow-up and are supported by an overall survival benefit.

Smith et al have calculated that the chances of the disease-free survival results losing significance are <20%.³ The primary concern regarding maintenance of the survival differences in that trial is that many patients in the control arm of this study are now crossed over to Herceptin, following the reporting of the 1-year follow-up statistics. If there are any uncertainties over the durability of the disease-free and overall survival benefits of 12 months therapy, these uncertainties must be many-fold higher for the 9-week therapy (FinHer) that has not been demonstrated to have a mortality benefit.

Metcalf et al also discuss minor methodological concerns in the different studies. In fact such analyses highlight the serious imbalance between the Herceptin and chemotherapy-alone arms in the FinHer study, including the findings that the patients in the non-Herceptin arms had more often less favourable characteristics, like larger tumour size, more grade 3 tumours, more oestrogen receptor-negative tumours and a slightly younger median age.

Further scrutiny of the FinHer study shows that only 33 of the 54 assigned to docetaxel with Herceptin actually received the protocol chemotherapy. This further highlights the risks associated with basing a funding policy on the results of a single small study and ignoring the results from a number of much larger trials. It is ironic that PHARMAC argue against a 12 month therapy, partly because they state the true long-term effects of 12-month therapy may never be known. In fact, this is because it is now viewed internationally to be unethical to continue studies where there is a control patient group without 12 months Herceptin treatment.

We remain perplexed as to why the Medical Advisory CaTSoP committee of PHARMAC was told that 12 months was not an option when considering their recommendations. We note that CaTSoP expressed a strong preference for 12 months of therapy, but were given the option of 9 weeks or nothing. Subsequent to the CaTSoP adjudications the evidence supporting 12 months treatment has further strengthened as studies continue to collect more follow-up data.²⁻⁴

Why, with CaTSoP's stated preference for 12 months of therapy did PETAC, the PHARMAC Board, and the DHBs not actively pursue additional funding from the Health Minister, rather than try to restrain spending within their current budget?

Health care is becoming inevitably more expensive with many other new drugs and technologies becoming available and offering potentially significant benefits. Beyond the issue of cost, if we do not adopt proven new therapies the quality of our care will inevitably fall further in comparison to other countries, at a time when our take up of new therapies is well behind most other OECD countries.⁸

In this setting, it is disappointing that PHARMAC appears unable to weigh up the narrow (drug costs), short-term fiscal imperative against available research evidence

together with the wider and longer-term health care costs, in a logical, systematic, and transparent fashion.

A major role for PHARMAC here, which has proven to be very effective in the past, should be to push for optimal pricing of Herceptin by negotiation with the pharmaceutical industry.

It is clear that Herceptin improves the outcome of patients with early stage HER2-positive breast cancer, but the current international standard of care remains 12 months of therapy. PHARMAC have now introduced a regimen for funded treatment on the basis of very poor evidence, which is one small trial with serious statistical concerns, in preference to regimens supported by robust clinical trial data.

While PHARMAC have a difficult job in balancing pharmaco-economic benefits of treatment, we believe in this instance they have placed too little weight on compelling scientific evidence. The risks they have taken with their decision to fund 9 weeks of Herceptin are not so much with their limited budget, but much more significantly with patients' lives.

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