

Herceptin

Questions and answers

May 2007

Funding of Herceptin

What have PHARMAC and District Health Boards agreed to fund?

PHARMAC and District Health Board have approved funding for Herceptin (trastuzumab), a monoclonal antibody drug, for the treatment of early HER2-positive breast cancer. Funding is for nine weeks of Herceptin therapy when it is given in combination with a taxane, such as docetaxel or paclitaxel.

Why nine weeks' treatment?

The Pharmacology and Therapeutics Advisory Committee (PTAC) recommended nine weeks' treatment, when given concurrently with a taxane, be funded with a high priority. While other treatment regimens may be as effective, nine weeks concurrent treatment is the option that provides the most health benefit relative to the cost.

Assessment of nine weeks' treatment is based on the successful FinHer trial, which combined Herceptin with the breast cancer treatment docetaxel.

The nine-week treatment is effective in reducing the chances of tumours returning, at a lower overall cost compared with the 12 month treatment regimen examined in other Herceptin clinical trials. This makes the nine week option the best value for money option.

What is the difference between a nine week and 12 month regimen?

The nine weeks of Herceptin is taken at the same time as taxane chemotherapy. Previously, PHARMAC was asked to consider a 12 month regimen *after* chemotherapy. This timing of treatment is a key factor.

In addition, the nine-week treatment:

- Has a lower overall dosage
- May be less toxic to the heart, although this requires further data
- Can be delivered immediately (once funding commences) by DHBs
- Is practical and affordable for District Health Boards.

Is nine weeks' therapy effective?

Yes. In a clinical trial setting the nine week concurrent treatment with Herceptin was shown to reduce the chances of tumours returning. Very similar clinical benefits have been shown in trials of both short duration (9 weeks) and long duration (12 months) therapy.

Why isn't the full 12 months treatment regimen being funded?

Nine week therapy with Herceptin is in itself a full treatment regimen. As described above, taking Herceptin in this way has been shown to be no less effective than longer duration treatment. Clinical trials have not established whether adding any further Herceptin treatments after 9 weeks can produce greater benefits. A study to test this question is in development internationally.

The funding decision provides a fully funded choice for women with HER2 positive early breast cancer. Other treatment options remain available, however only the nine-week concurrent treatment regimen will be publicly funded.

Is there a biological rationale for using concurrent treatment?

Yes. Herceptin is one of the class of drugs called monoclonal antibodies, which are used to treat conditions such as cancers, arthritis and auto-immune disorders. While effective on their own, monoclonal antibodies are sometimes more effective when used in combination with other agents. This "synergistic" benefit of

Herceptin in combination with taxane chemotherapy is seen when it is used in metastatic breast cancer, where data indicates that Herceptin is more effective when used concurrently with other chemotherapy, rather than on its own.

In early breast cancer, concurrent treatment also appears to have an improved benefit (better disease free survival rates) over sequential (after chemotherapy) treatment.

How can women access the funded treatment?

Women who are eligible for Herceptin will need to give informed consent for the subsidised treatment; this is required because the nine weeks concurrent therapy is not currently approved by Medsafe. Access to treatment in this way (under section 25 of the Medicines Act) is already commonly used for cancer drugs. PHARMAC will also develop resources for women with breast cancer, to help them understand more about breast cancer (including HER2-positive breast cancer).

Herceptin is a chemotherapy drug delivered in public hospitals, so there will be no cost to patients for having the funded treatment.

What will it cost DHBs to fund nine weeks' therapy?

Funding the nine-week treatment regimen for all eligible NZ women would cost about \$6 million per year (including DHB service cost).

How many women will be eligible for treatment?

About 350 women each year will be eligible for treatment with Herceptin for 9 weeks when given concurrently with a taxane.

General background

What is happening in other countries?

A number of other countries have approved funding for Herceptin, using a 12-month treatment regime. In some of those countries, assessment of funding for a medicine is limited to how the company applies for it to be used.

However, there are variations throughout the world in the way Herceptin is used. In the United States, Herceptin is approved for use concurrently with paclitaxel (a taxane). In Europe, however, it can only be approved for use on its own after completion of all chemotherapy. In Australia, clinicians have a number of approved options for using Herceptin including long (12 months) and short duration (9 weeks), and using it concurrently with, or after, chemotherapy.

Why is NZ choosing a different path to other countries?

Pharmaceutical funding in New Zealand takes place within a budget, so choices have to be made about how to allocate spending most effectively to ensure that the best health outcomes possible from medicines are achieved for all New Zealanders. Most other countries, including the UK and Australia, do not have such a budget and prioritisation process.

In the UK, the National Institute for Health and Clinical Excellence (NICE) makes its recommendations independent of budget considerations. However, debate in the UK is now suggesting that funding Herceptin will force the National Health Service to cut some other health services, underlining the need for careful choices to be made¹.

This is not the first time NZ has chosen a different path to other countries. In 2004, PHARMAC declined funding for the class of arthritis medicines known as Cox-2 Inhibitors, citing concerns over their safety profile and high cost. Two of the Cox-2 drugs have subsequently been withdrawn internationally because of safety concerns. PHARMAC also took a different approach in regard to Cerezyme, an enzyme replacement drug,

¹ How much will Herceptin really cost? *BMJ* 2006;333:1118-1120 (Ann Barrett, Tom Roques, Matthew Small and Richard D Smith)

choosing a lower dosage level than was then international practice. Hindsight has shown this to be the correct approach.

How many clinical trials have been conducted on Herceptin?

PHARMAC is aware of six trials looking at Herceptin for HER 2 positive early breast cancer. Five of these trials included Herceptin in combination with other therapy, while one trial – HERA (and one arm of another) – looked at Herceptin on its own (sequential treatment, or after chemotherapy).

What does the evidence in clinical trials on Herceptin show?

The two-year median follow-up data from HERA show that the absolute increase in disease-free survival was 6.1%, and that 1.8% more people were still alive compared with the control group (chemotherapy only). In other words, one year after completing their 12 months course of Herceptin, one in every sixteen people treated avoided (delayed) having their breast cancer recur compared with those who did not receive Herceptin, and one extra death was avoided (delayed) for every 55 people treated. However, two-year follow-up is relatively short, and whether or not these results translate to longer term benefits remains to be determined. It should be noted that the differences between the control group and the Herceptin treated group were less at two-year median follow-up than at one-year median follow-up, therefore, there are legitimate questions regarding the durability of the effectiveness of Herceptin.

Results from the FinHer (9 weeks) study were comparable to those obtained in the HERA trial (11.7% absolute reduction in disease recurrence at three years median follow-up, compared to the control group). In other words, about 34 months after completing Herceptin chemotherapy, one in every 8-9 people treated had delayed having their breast cancer recur (compared with no Herceptin). The FinHer trial also reported no severe heart failure, although the study may not have been of sufficient size to detect this effect.

Does Herceptin improve overall survival in patients with HER 2 positive breast cancer?

12 month regimens for Herceptin have been shown in clinical trials to statistically significantly improve overall survival (all causes of death).

The 9 week concurrent regimen of Herceptin has also shown to improve overall survival but those early results did not reach statistical significance. This effect is similar to the early interim analysis of the HERA study at 12 months, published in the New England Journal of Medicine in 2005 (Piccart-Gebhart et al.), whose survival improvements at that time were also not statistically significant. Whilst awaiting further confirmatory results from FinHer, it is reasonable to assume that the statistically significant improvements in disease free survival seen for the 9 week regimen will lead to improvements in overall survival. Significant results for overall survival in FinHer may become available later this year.²

Has the cost-effectiveness of Herceptin been estimated?

Yes. PHARMAC estimates the cost in economic terms of a nine-week combination treatment of Herceptin to be less than \$20,000 per QALY³ (or 50 QALYs per million dollars spent). At less than \$20,000 per QALY, Herceptin is as cost-effective as many other medicines PHARMAC has funded. This compares with a cost per QALY of about \$75,000 for the 12-month regimen.

² Statistically significant improvements in disease free survival correlate with statistically significant improvements in overall survival in studies of longer duration Herceptin. The results of the FinHer Trial (as published in the NEJM in 2006) were a pre-planned early interim analysis, pending final analysis at five years median follow-up (or 150 events overall, whichever occurring earlier). Overall survival in FinHer may have become statistically significant by around January 2004, and may become evident in the final 5-year median follow-up analysis of FinHer later in 2007.

³ A QALY ('quality-adjusted life year') is a standard economic measure, which combines 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.