

Pharmaceutical Management Agency

Summary of Submissions

on PHARMACs Proposal to Decline Funding
for 12 months treatment with Herceptin for
HER 2 positive early breast cancer

August 2008



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INTRODUCTION

We recently sought public comments on a proposal to decline the funding of 12 months treatment (sequential or concurrent) with Herceptin for HER2-positive early breast cancer. Responses to this consultation formed part of the information that the PHARMAC Board considered when reaching its decision on the proposal, to decline funding for 12 months Herceptin, announced on 7 August 2008.

This *Summary of Submissions* document provides background information about why we undertook consultation, describes the consultation process and provides a summary of the submissions we received. The views that stakeholders expressed in their submissions are described in general terms. PHARMAC also provides some response comments on the key themes that submitters' raised. It is important to note at the outset that this summary is not intended as a replacement for the individual submissions themselves; all of which stand in their own right. All responses were individually provided to and considered by the PHARMAC Board, as part of the decision making process. Copies of the actual individual submissions received are available from PHARMAC on request.

Further information can be found on our website (www.pharmac.govt.nz) including the following:

- Media Release announcing PHARMACs decision regarding the proposal to decline funding of 12 months Herceptin treatments
- A summary of the clinical evidence
- Herceptin Q&A
- Pharmacology and Therapeutics Advisory Committee (PTAC) minutes from 4 July 2008
- Cancer Treatments Subcommittee of PTAC (CaTSoP) minutes from 13 June 2008
- An updated cost utility analysis

The resources for patients will also be updated in the coming weeks to include new clinical evidence and information about the confidence in the evidence.

BACKGROUND

Why we undertook consultation

In July 2006, PHARMAC made a decision not fund Herceptin for HER2-positive early breast cancer patients, at that time, pending further investigative work. In April 2007 PHARMAC made a decision to fund a concurrent 9 week treatment regimen of Herceptin for the treatment of HER2-positive early breast cancer patients. In April 2008, the High Court ruled on a Judicial Review of our processes surrounding these, and other, decisions related to Herceptin funding.

The Court found that we should have consulted prior to our July 2006 decision. The Court found that this decision was a decision to decline Roche's application for funding for 12 months sequential treatment with Herceptin. Because of the failure to consult, the Court set that decision aside and directed us to make a new decision regarding the application, following consultation.

PHARMAC's April 2007 decision to fund a concurrent 9 week treatment regimen of Herceptin for HER2-positive early breast cancer patients was found by the Court to not to be unreasonable or irrational in any legal sense, and this decision remains in place.

The consultation process

In May this year, we distributed a consultation letter regarding our proposal to decline the funding of 12 months treatment (sequential or concurrent) with Herceptin for HER2-positive early breast cancer to those groups and individuals that, in our view were likely to be most affected by the proposal. We also posted the consultation letter on our website and issued a media release so that anyone with an interest could provide a response. A copy of that consultation letter is attached as **Appendix 1** to this *Summary of Submissions* and can be found on our website at www.pharmac.govt.nz.

Rather than using an open ended question such as "should PHARMAC fund 12 months Herceptin", the consultation letter stated that our proposal was to decline the funding of 12 months treatment. Good consultation is best achieved through clarity about a proposed approach, so when we consult on a funding application we are specific about our proposal. This is a transparent way to go about consultation which, in our view, best enables interested groups to provide meaningful responses on how the proposal may impact on them. We emphasised in the consultation letter that consulting on a specific proposal did not reflect that we had already made a decision, and we were explicit that the view we consulted on might change as a result of consultation.

We also explained in the consultation letter that our role was not to 'count votes' but rather to ensure that the PHARMAC Board would consider all relevant information about the potential effects of the proposed approach, before reaching a decision.

We encouraged people responding to consultation to provide reasons supporting their views. We noted in particular that comments on the comparative risks and benefits between 9 weeks and 12 months (sequential or concurrent) Herceptin treatment regimens would be helpful.

As well as inviting written submissions, we met face to face with a number of groups who had previously expressed a strong interest in our funding decisions relating to Herceptin.

Consultation Responses

We received a total of 319 responses to our consultation. We appreciate the time it takes for people to make submissions, and the personal and emotional nature of the issues that consultation on this topic raised. We are grateful to everyone who made the effort to provide us with their views.

A list of the groups and organisations that made submissions is included in **Appendix 2** to this *Summary of Submissions*. Details of some individuals who made submissions are not disclosed, to protect their privacy.

Copies of the full consultation submissions have been released to individuals who have requested them under the Official Information Act 1982 (with the names of some individuals withheld to protect their privacy), and are available from us on request (which can be made via email to herceptin submissions@pharmac.govt.nz).

PURPOSE

The purpose of this *Summary of Submissions* document is to reflect the overall messages that submitters communicated to us in relation to the proposal, and to provide some response comments on the key themes that were raised. Being a summary, the level of detail that individual submitters provided in their submissions is not necessarily reflected. We have made every effort to accurately reflect the views of submitters but reiterate that, to gain the fullest understanding of submitters' perspectives, this summary is not a substitute for reading the full submissions themselves.

Similarly the comments we provide do not necessarily address all the views raised in submissions or all the information relevant to the themes raised. We have tried to provide as much information as possible to explain the rationale for our decision on the Herceptin proposal both in the response comments sections of this document, and in other information available on the Herceptin page of our website. Please contact us if you have any questions about any specific points that are not addressed in the *PHARMAC Comments* sections of this document.

KEY THEMES

We found that the responses we received could be categorised into 13 key themes. Submitters views on these themes are summarised below, and our comments on the key points raised are included at the end of each section.

The following 9 of these themes were directly related to PHARMAC's proposal to decline funding for 12 months treatment with Herceptin:

1. The proposal to decline 12 months funding
2. The MedSafe Registration status of the concurrent 9 week treatment
3. HER2-positive breast cancer in the New Zealand population
4. HER2-positive breast cancer in Māori and Pacifica Women
5. The evidence for the effectiveness of various Herceptin treatment options
6. The cardiac side effects of Herceptin
7. The Cost-effectiveness and cost of Herceptin
8. Legality of PHARMAC's process
9. The impact of HER2-positive breast cancer on women, including personal stories from women with breast cancer and their families and friends

The following four themes raised related to broader concerns about the New Zealand medicines funding framework and the context in which funding decisions are made:

10. International comparisons
11. Government prioritisation of health spending
12. PHARMAC's funding processes
13. The role of media and advocacy groups

Some of the views submitters expressed in relation to these four themes were raised during the development of the Government's *Medicines New Zealand* medicines strategy in 2006-2007, and some feature the national and international media. These themes are outside of the scope of the specific Herceptin proposal that we consulted on. However they were taken into account by PHARMAC prior to making its decision and, for completeness, we have summarised the views expressed and provide our comments below.

Key themes directly relevant to the Proposal Consulted on

1. The proposal to decline 12 months funding

Submitters' views

The majority of submitters did not support our proposal to decline funding for 12 months treatment (sequential or concurrent) with Herceptin for HER2-positive early breast cancer. These submitters considered that the 12 month regimen should be funded instead of the currently-funded concurrent 9 week Herceptin regimen. Some submitters suggested that women and their oncologists should be able to choose the appropriate length of treatment (9 weeks or 12 months). Some submitters considered that funding of Herceptin for advanced/metastatic HER2-positive breast cancer should be stopped in order to fund 12 months Herceptin for HER2-positive early breast cancer.

The view was also expressed that 12 months Herceptin should be funded now with the provision for reviewing this decision when more information comparing the effectiveness of the 9 weeks and 12 month regimens becomes available in the future.

A minority of submitters supported PHARMAC's proposal to decline funding for 12 months treatment. These submitters either considered that the 12 months treatment regimen is no more effective than the 9 week treatment regimen, or that any additional benefit offered by 12 months treatment (sequential or concurrent) over the concurrent 9 week treatment regimen is not justified because of safety concerns with the 12 month treatment regimen and/or the increased costs. The view was also expressed that in the context of the New Zealand health care system, and the budget constraints faced by DHBs, a cautious approach to the funding of Herceptin was justified, particularly when the publicly available Herceptin evidence is affected by publication bias.

Responding DHBs supported the proposal to decline funding for 12 months treatment with Herceptin. They expressed the view that, in the absence of advice which provides DHBs with alternative compelling information, there is no current basis for them to revisit their support of the funding of the concurrent 9 week treatment regimen.

PHARMAC comments

In order to recommend funding of 12 months Herceptin PHARMAC would need to be confident that it offered sufficient additional health benefits over the currently funded concurrent 9 week treatment, and that investing in those benefits would not displace other medicine funding options associated with greater health gains. We are not satisfied that this is the case.

The available clinical evidence for Herceptin in HER2-positive early breast cancer only allows for indirect comparisons of the risks and benefits of the various different treatment regimens; new clinical trials such as SOLD which compares concurrent 9 weeks and 12 months treatments are needed for direct comparisons.

Herceptin does provide some additional benefit and risks for some patients over standard chemotherapy treatment for HER2-positive early breast cancer in the short term. Data is continuing to emerge about the magnitude of these benefits and risks and how long they last. In general longer term follow-up data on these studies suggest the benefits may lessen over time. No head-to-head trials have shown whether long or short duration therapy is more effective.

Adjuvant Herceptin in early breast cancer can be given in two main sequences: concurrently with or sequentially after other chemotherapy. The main body of evidence for Herceptin in HER2 positive early breast cancer comprises four studies examining concurrent treatment (NCCTG N9831^{1 2 3}, NSABP B-31^{2 3}, BCIRG006⁴, and FinHer⁵) and three studies examining sequential treatment (HERA^{6 7}, NCCTG N9831¹ and PACS04^{8 9}). Here is a summary of the results of these main trials:

- HERA (sequential 12 months treatment) – when measured after 2 years, compared with standard chemotherapy, for every 100 women treated with Herceptin, six more would avoid having their tumours recur or death (disease events), and nearly two extra deaths from any cause would be avoided.

-
1. Perez EA, Suman VJ, Davidson N, et al on behalf of NCCTG, ECOG, SWOG, CALGB. Further analysis of NCCTG-N9831, May 2005 update. Slide presentation presented at the 45th annual meeting of the American Society of Clinical Oncology, Orlando, FL, USA, May 13–17, 2005. http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Virtual+Meeting?&vmview=vm_session_presentations_view&confID=34&sessionID=934.
 2. Romond, EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER-2 positive breast cancer. N Engl J Med 2005; 353: 1659-72. <http://content.nejm.org/cgi/content/full/353/16/1673>; on-line supplementary appendix at <http://content.nejm.org/cgi/data/353/16/1673/DC1/1>
 3. Perez EA, Romond EH, Suman VJ, et al, NCCTG/NSABP. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer. 2007 ASCO Annual Meeting Proceedings Part I. J Clin Oncol 2007; 25 (suppl 18): 512 (abstr). http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnnextoid=76f8201eb61a7010VqgVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=47&abstractID=35229
 4. Slamon D, Eiermann W, Robert N, et al, on behalf of the BCIRG 006 Investigators. Phase III Trial Comparing AC-T with AC-TH and with TCH in the Adjuvant Treatment of HER2 positive Early Breast Cancer Patients: Second Interim Efficacy Analysis. Slide presentation ASCO annual meeting 2006, available online at <http://www.bcirg.org/NR/rdonlyres/eqkdodg2dy7t557o7s6uvj7ytpe6gcfq5qmh2ely6hnhh5pjlaz3nd6jddlnao7goikej3edohsjyisfvp367uuc/BCIRG%20006+2nd+Interim+Analysis.pdf>
 5. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, et al; FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354:809-20. <http://content.nejm.org/cgi/content/full/354/8/809>
 6. Piccart-Gebhart M.J. Procter M, Leyland-Jones B, et al, for the Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659-72. <http://content.nejm.org/cgi/content/full/353/16/1659>
 7. Smith I, Procter M, Gelber RD, et al, for the HERA study team. 2 year follow up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007; 369: 29-36. <http://www.thelancet.com/journals/lancet/article/PIIS0140673607600282/fulltext>
 8. Spielmann M, Roché H, Humblet Y, et al. 3-year follow-up of trastuzumab following adjuvant chemotherapy in node positive HER2-positive breast cancer patients: results of the PACS-04 trial. San Antonio Breast Cancer Symposium, San Antonio, TX, USA, December 13-16, 2007. http://www.abstracts2view.com/sabcs/view.php?nu=SABCS07L_661 (accessed May 11, 2008).
 9. Spielmann M, Roché H, Humblet Y, et. al. Trastuzumab following adjuvant chemotherapy in node positive, HER2-positive breast cancer patients: 4-year follow-up results of the PACS-04 trial. San Antonio Breast Cancer Symposium, San Antonio, TX, USA, December 13-16, 2007. <http://www.sabcs.org/> Daily Slide Reviewer: Presentations: Day 4: General Session 7 (accessed May 11, 2008).

- NCCTG N9831 Arm B (sequential 12 month treatment) – no benefit (a 1.5% improvement in disease-free survival, which was not significantly better than standard chemotherapy) after 18 months.
- PACS04 (sequential 12 month treatment) – no benefit (a 3.4% improvement in disease-free survival, which was not significantly better than standard chemotherapy, a -0.4% benefit for overall survival, statistically worse than standard chemotherapy) after 4 years.
- Romond/Perez studies, combined data from NCCTG N9831 Arm C and NSABP B-31 (concurrent 12 months treatment) – for every 100 women treated with Herceptin compared with standard chemotherapy, nearly 9 would avoid having their tumours recur or death (disease events), and nearly 3 additional deaths from any cause would be avoided (measured at 3 years follow up).
- BCIRG006 (concurrent 12 months treatment) – for every 100 women treated with Herceptin compared with standard chemotherapy, 6 would avoid having their tumours recur or death (disease events), and nearly 3 additional deaths from any cause would be avoided (measured at 3 years follow up).
- FinHer (concurrent 9 weeks treatment) – for every 100 women treated with Herceptin, compared with standard chemotherapy, nearly 13 more women would avoid having their tumours recur or death (disease events), when measured after three years.

PHARMAC's Pharmacology and Therapeutics Advisory Committee (PTAC) (<http://www.pharmac.govt.nz/healthpros/PTAC>) and its Cancer Treatments subcommittee (CaTSoP) reconsidered the clinical evidence at their 4 July 2008 and 13 June 2008 meetings respectively, the minutes from these meetings can be found on our website www.pharmac.govt.nz. PTAC considered that there was still uncertainty about the best way of administering trastuzumab in terms of optimal treatment sequencing, duration, minimising cardiovascular toxicity, and long-term clinical outcomes. The optimal treatment regimen in HER2-positive early breast cancer cannot be determined from the current evidence. Only indirect comparisons of the various trials can be drawn. A brief summary of the available evidence for Herceptin in HER 2 positive early breast cancer can be found in **Appendix 4** to this *Summary of Submissions*, a more extensive summary of the evidence can be found on our website www.pharmac.govt.nz.

PTAC, having reviewed the evidence, recommended that funding of a 12 month regimen (either sequential or concurrent) should be declined. It also stated that no new information had been presented that demonstrated any additional health benefit for 12 months treatment (sequential or concurrent) over the currently funded concurrent 9 week regimen. Emerging evidence is that sequential 12 months is the least effective way to use Herceptin trastuzumab. PTAC noted that although the weight of evidence supports the use of concurrent 12 months trastuzumab, there are on balance overriding concerns about its durability of efficacy, increased cardiotoxicity, its high cost, and the lack of conclusive evidence of additional health gain over the 9-week regimen. Both PTAC and CaTSoP recommended that the funding for concurrent 9 week trastuzumab be continued.

PHARMAC is not confident that there would be additional health gains from funding a 12 month regimen (concurrent or sequential) compared with the currently funded concurrent 9 week regimen. On the basis of the indirect comparisons from current trial evidence and the advice we have received from PTAC, we think it is reasonable to assume that 12 month treatments may produce no additional health gain compared with the funded concurrent 9 week regimen.

The decision to fund Herceptin for metastatic HER2-positive breast cancer was not made using PHARMAC's normal funding processes. In 2001 the Ministry of Health published a report, *Improving Non-Surgical Cancer Treatment Services in New Zealand*, which, in an attempt to address national inconsistencies in access, listed cancer drugs that should be consistently available in all New Zealand cancer treatment centres. This list has come to be known as the "oncology basket", and it included Herceptin for metastatic HER2-positive breast cancer. In late 2001 PHARMAC was authorised by the Minister of Health to perform an additional function (in addition to those set out in s48 of the New Zealand Public Health and Disability Act 2000), being "to manage the purchasing of any or all pharmaceuticals, whether used in hospitals or outside it, on behalf of DHBs". Soon after being authorised to perform this function PHARMAC listed the "oncology basket" pharmaceuticals on the Pharmaceutical Schedule, including Herceptin for treatment of metastatic HER2-positive breast cancer.

2. Medsafe Registration status of the funded concurrent 9 week treatment

Submitters' views

Some submitters noted that the funded concurrent 9 week Herceptin treatment regimen is not approved by Medsafe, and in their view it is therefore unethical to fund this treatment regimen. The view was expressed that the 'disclaimer' that women needed to sign to receive the concurrent 9 week treatment was aimed at protecting PHARMAC's back.

The comment was also made that the funded concurrent 9 week treatment is not approved by any international regulatory body which is equivalent to Medsafe, and nor is it recommended to in any prescribing documents/guidelines. Another submitter commented that a successful appeal in Australia means that the concurrent 9 week treatment, which the Australian Therapeutic Goods Administration (the Australian equivalent of Medsafe) had previously approved, is to be removed from the Australian datasheet that specifies the approved treatment regimens.

PHARMAC comments

Current provisional registration of Herceptin in New Zealand

Herceptin is currently provisionally approved by Medsafe for *up to* 12 months treatment following completion of surgery and chemotherapy (ie *up to* 12 months sequential treatment) in HER2-positive early breast cancer. Concurrent treatment (9 weeks or 12 months) is not approved. Roche (the supplier) applied, and received provisional approval, for a regimen of sequential treatment in New Zealand based on data from the HERA study. Approval by regulators relates to the ability of a supplier to market their product in a particular way.

This Medsafe approved regimen (12 months sequential) is different from that approved in some other countries. In the United States, for example, Herceptin is approved for both concurrent and sequential use, and in Australia it is approved for use "in association with chemotherapy", approving marketing by Roche of 12 months' sequential, 12 months' concurrent or 9 weeks' concurrent treatment regimens.

We note that the FinHER study (9 weeks concurrent) was published after Medsafe had completed its evaluation of the safety, quality and efficacy of Herceptin in early breast cancer and was not reviewed by Medsafe when it gave Herceptin provisional approval. At a meeting regarding whether to grant Herceptin full consent, MedSafe's Medicines Assessment

Advisory Committee (MAAC), identified that evidence of the safety and efficacy of Herceptin when used in different dose regimens, treatment sequences and durations of treatment is still accumulating. MAAC asked Roche to supply further evidence in support of the use of Herceptin in early breast cancer treatment before it could be considered for full consent. Roche has yet to provide this information.

In March 2007 the Chair of PTAC wrote to Medsafe and stated his hope that there would be an opportunity for Medsafe to review the Datasheet for Herceptin and align it with the Australian Datasheet. The record of the meeting records that MAAC 'had expressed concerns about the uncertainty about the optimum dose and frequency of dose for early stage breast cancer, and as a result, had written to the company requesting more data to justify the sequence of use and the dosage regimen for early breast cancer' and that the 'data provided by PHARMAC addressed the same questions the Committee had already asked of the company. Some of the data provided by PHARMAC were unpublished data. MAAC considered there were insufficient data of a regulatory quality and quantity to justify a change in the existing indication. Medsafe does not consider unpublished data.

The different roles of PHARMAC and Medsafe

The Medsafe registration process and PHARMAC's funding process fulfil two different functions. The purpose of the Medsafe process is to consider material provided by a pharmaceutical supplier on a particular treatment to determine the quality, safety and efficacy of the treatment for the purposes for which it is to be marketed. Medsafe determines which treatments can be sold by suppliers in New Zealand. Medsafe considers information provided to it by the pharmaceutical supplier. It is concerned mainly with the efficacy and safety of a new treatment in comparison to "no treatment" or standard care.

On the other hand, PHARMAC determines which of the medicines that are available in New Zealand will receive a subsidy, and considers *relative* efficacy, safety, cost-effectiveness and budgetary impact compared to already funded treatments, among other factors, when making these decisions. PHARMAC is entitled to consider information provided by the pharmaceutical supplier and any other information that is available through its own research and via its clinical advisory committees.

Put simply, Medsafe assesses absolute efficacy and safety – is it safe? does it work?; PHARMAC assesses *relative* efficacy specific to relevant population groups and compared with other funded treatments or other treatments awaiting funding.

Prescribing 'off-label'

Medsafe's regulatory approval deals with which products a company can market, and how they can do that. Section 25 of the Medicines Act 1981 specifically allows doctors to prescribe treatments for indications, or treatment regimens, which have not been approved by Medsafe. Doctors are required to obtain informed consent from their patients when prescribing treatments under Section 25. Because the funded concurrent 9 week regimen is not approved by Medsafe, doctors need to rely on Section 25 of the Medicines Act to prescribe the funded treatment. In oncology, as with some other areas of medicine, the practise of 'off-label' prescribing is not uncommon, with rates stated to be up to 40% in adults and up to 90% in paediatric patients.¹⁰ It is permitted both legally and ethically, so prescribing of concurrent 9 weeks Herceptin is not unique in this respect. It is, however, uncommon for PHARMAC to specifically fund a treatment regimen that hasn't been approved

¹⁰ Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: consensus recommendations for evaluating appropriateness. Med J Aust. 2006 Nov 20;185(10):544-8.
http://www.mja.com.au/public/issues/185_10_201106/gaz10250_fm.html

by Medsafe; we have done so in this case because of the magnitude of benefit demonstrated for the concurrent 9 week treatment for the relatively low cost in obtaining that benefit. Also relevant is the fact that Herceptin is approved in NZ for only sequential treatment of early breast cancer, whereas overseas it is specifically approved for concurrent administration.

Australian Registration

Until recently the Australian Product Information sheet included a statement that the optimal dosage regimen and treatment duration for Herceptin have not been defined. The Product Information sheet further stated that a favourable risk/benefit ratio had been demonstrated with a number of regimens' including 12 months sequential (the HERA trial), 12 months concurrent (B31/N9831 trial) and concurrent 9 week (FinHER).

Roche recently applied to the Australian Therapeutic Good Administration (TGA) to have the concurrent 9 week (FinHER) information and regimen removed from the Australian Product Information sheet. The TGA declined the application but agreed that there was some merit in Roche's argument that it is not appropriate for the FinHER data to be given equal prominence as the 12 month treatment data in the Product Information sheet. As a result, the TGA agreed to remove actual FinHER data from the Product Information sheet. The TGA has, however, added the following statement to the Australian Product Information sheet:

'the optimal duration of adjuvant Herceptin is not known and may be clarified only in further randomized trials. Outcomes of an alternative dosage schedule involving treatment for 9 weeks are reported in a published paper of trial data (ref FinHER).'

The TGA evaluator who assessed Roche's application said he agreed with the Australian Drug Evaluation Committees (ADEC) view that 'the results of FinHER suggest it is possible that short term treatment may provide comparable efficacy [to 12 months] with less cardiac toxicity'. He also noted that the UK SchARR report (a report commissioned by NICE on the cost effectiveness of Herceptin) had noted that 'FinHER may facilitate lower cost, greater patient convenience and reduced risk of cardiotoxicity'.

Summary

In summary, the Medsafe and PHARMAC processes are separate and undertaken for different reasons. Medsafe has given provisional consent to the use of Herceptin for HER2-positive early breast cancer as a sequential treatment, on the basis of the material provided to it by Roche. Medsafe has requested more information from Roche regarding the optimum treatment regimen for Herceptin. To date, MedSafe has not been provided with sufficient data of a regulatory quality and quantity to enable it to make a decision on whether to give the treatment of HER2-positive early breast cancer with Herceptin full consent.

3. HER2-positive breast cancer in the New Zealand population

Submitters' views

One submitter, a private breast cancer clinic, expressed the view that the number of HER2-positive patients in the New Zealand population may have been overestimated. In support of this, the submitter noted differences in records of the percentage of breast cancers that are HER2-positive.

Specifically, the submitter drew to our attention that the Auckland Cancer Register for June 2000 to December 2005 showing that 22% of breast cancers were HER2-positive and a review of the Register from 1 January 2005 to 31 May 2008 showing only 17% HER2-positive breast cancers. In comparison, the submitter noted that data from their private clinic from 1 January 2005 to 31 May 2008 showed that only 12.15% of breast cancers were HER2-positive.

The submitter suggested that it may be cost-effective to retest all HER2-positive patients identified by immunohistochemistry (IHC) with fluorescent in situ hybridisation (FISH) testing as some of the patients might not be truly HER2-positive.

PHARMAC comments

PHARMAC's analysis of the rates of HER2-positive breast cancers was based on New Zealand Health Information Survey data. Our analysis shows rates of HER2-positive breast cancers for 2005 similar to those recorded by this submitter. This reflects, in part, higher testing rates in recent years, with an associated decline in the proportion of breast cancers detected that are HER2-positive.

Further information on the prevalence of HER2-positive breast cancer is available in the PHARMAC-authored NZ Medical Journal article of June 2007 Appendix 2: *Epidemiology of HER2-positive breast cancer in New Zealand, with ethnic/regional disparities*¹¹. We are not aware of the generation of any substantive new evidence on the prevalence of HER2-positive breast cancer since the appendix to the article was written.

We acknowledge that there are considerable uncertainties around the incidence of breast cancer patients, the number of HER2-positive patients, and the uptake of Herceptin treatment. We have used a range of possible values for the number of patients treated when considering funding to ensure that various potential scenarios are tested.

We have not assessed the impact of FISH testing compared with IHC HER2-positive testing protocols on the number of patients who may be treated. Protocols regarding HER 2 testing methodology are determined by DHBs and clinicians independent of PHARMAC.

4. HER2-positive breast cancer in Māori and Pacifica Women

Submitters' views

A number of submitters remarked on the increased prevalence of HER2-positive breast cancer in Māori and Pacifica women, and the implications of this for our proposal.

Submitters commented that Māori and Pacifica women have a particularly high level of HER2-positive breast cancer, are diagnosed at a later stage than women of other ethnicities, and access private health care less frequently.

It was noted that the "particular health needs of Māori and Pacific peoples" is one of PHARMAC's nine decision making criteria. The views were also expressed that not funding 12 months Herceptin is likely to impact on Māori and Pacifica significantly, and that by funding concurrent 9 week Herceptin only and not funding 12 months Herceptin disparities

¹¹ 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>

between Māori/Pacific women and other ethnicities would increase and PHARMAC would be failing to fulfil its Treaty of Waitangi obligations.

An alternative perspective, which was suggested, was that given the current disparities that exist between different ethnic groups, it would be more efficient and ethical to fund the concurrent 9 week regimen and apply the 'savings' made from not funding the 12 month course to address these inequalities in other ways, e.g. increased breast screening for Māori and Pacific women. One submitter considered that breast cancer followed an 'inverse' socio-economic gradient and therefore spending more money on Herceptin would simply increase inequalities as it would benefit those on the higher end of the socio-economic scale ie NZ Europeans, not Māori and Pacific women.

PHARMAC comments

We agree that Māori and Pacific women have a higher incidence of HER2-positive breast cancer, are generally diagnosed with later stage disease and access private health care less frequently than women of other ethnicities.

Submitters identified 'the Particular needs of Māori and Pacific people' as one of PHARMAC's nine decision criteria. Our commitment to Te Tiriti o Waitangi is reflected in our Māori Responsiveness Strategy (2002), Te Whaioranga Māori Health Action Plan (2008), and in the PHARMAC Operating Policies and Procedures (2006).

We seek to ensure that Māori and Pacific people enjoy the same access to medicines as non-Māori and non-Pacific. Our analysis of dispensing data indicates that the areas of greatest access and health status disparity in Māori and Pacific people relate to the use of antibiotics, newer antidepressants, statins, ACE inhibitors/A2 antagonists, and low dose aspirin (cardiovascular risk), but not to cancer medications.

To date no evidence has been generated that shows whether the provision of publicly-funded Herceptin (9 weeks or 12 months) would improve or worsen the existing disparities in incidence, later stage presentation, mortality and case fatality rates in Māori and Pacific women relative to other ethnic groups. Similarly, there is no evidence that 12 months treatment with Herceptin confers additional health benefits to the currently fully funded concurrent 9 week treatment, be it for Māori/Pacific or non-Māori/Pacific women.

Further information on the epidemiology of HER2 positive early breast cancer in Māori and Pacific women is available in Appendix 2 to the NZ Medical Journal article of June 2007 (referenced above). We are not aware of any substantive new evidence since that time.

5. Evidence for the effectiveness of various Herceptin treatment options

Submitter's views

Submitters' expressed their views about the evidence for the various different treatment options for Herceptin (12 months, sequential or concurrent, and 9 weeks concurrent). The conclusions that submitters' suggest should be drawn from the evidence were in some cases contradictory, reflecting the complexity of the evidence. Broadly the comments can be categorised into the following five groups:

1. the evidence for Herceptin in HER2-positive early breast cancer;

2. the evidence supports that 12 months treatment is better than 9 weeks treatment;
3. the evidence supports that concurrent 9 week treatment is as effective as 12 months treatment;
4. the evidence is not clear on the best treatment option; and
5. further research is required to determine the best treatment option.

Additionally, some breast cancer patients commented on the advice they had received from their oncology specialists on the best treatment option for them.

Details of the comments that submitters' made on evidence are described under these headings below.

The evidence for Herceptin in HER2-positive early breast cancer

Some submitters considered that the short term benefits for Herceptin mirror the disease free and absolute survival curves for other types of adjuvant chemotherapy suggesting the benefits of Herceptin are likely to increase over time. Other submitters noted that the current benefit of Herceptin measured over 2-3 years is still only a short timeframe and therefore it cannot be assumed that Herceptin represents a long term cure for HER2-positive early breast cancer.

One submitter noted that whilst it is recognised that Herceptin has a definite benefit for HER2-positive women with early breast cancer, its effect can, at best, be described as returning their risk to that of women with HER2 *negative* early breast cancer.

Evidence supporting that 12 months treatment is better than 9 weeks treatment

Some submitters considered that the evidence demonstrated that the 12 months treatment regimen (sequential and/or concurrent) was the most effective treatment and was better than the funded concurrent 9 week treatment. The main reasoning for this conclusion was that, because there were more patients treated with a 12 month regimen of Herceptin in clinical trials than with concurrent 9 weeks, the evidence for 12 months treatment is better; and therefore the concurrent 9 week treatment evidence should not be relied upon. The view was expressed that in funding the concurrent 9 week treatment, PHARMAC was recommending an unproven regimen.

Some submitters criticised attributes of the FinHER (concurrent 9 week treatment) study design and data that, in their view, meant that it should not be relied on. These included views that FinHER:

- was hypothesis generating and should not be the basis of a funding decision;
- lacked statistical robustness and power;
- did not include enough patients (and thus the number of disease recurrence events was too small);
- was not accompanied by corroborative data from other studies;
- was biased due to unbalanced prognostic indicators and other confounding factors; and
- demonstrated no statistically significant improvement in overall survival.

Further, one submitter expressed that the detailed study documentation was not available for review, and that there was a 1:20 chance that the FinHER study result was a 'false positive'.

In addition, one submitter noted that PHARMAC had agreed to alter its Herceptin patient information leaflets to highlight FinHER's wide confidence intervals with respect to disease free survival benefit.

Views were also expressed about the strength of other evidence. Specifically, that the negative data from the 12 month sequential treatment arm of study N9831 does not negate the positive data from the HERA trial (12 months sequential treatment), and that negative data from the study PACS04 (12 months sequential treatment) cannot be relied upon because it had a small sample size, 10% of participants got no treatment, and 18% of participants stopped treatment prior to 30 weeks.

The following quote from the St Gallen International Expert Consensus Guidelines was included in a submission to support the use of 12 months treatment with Herceptin over concurrent 9 week treatment with Herceptin:

“The standard duration of Herceptin therapy was accepted as 1 year. A shorter duration (9 weeks) as used in the FinHER study was not generally accepted”¹²

The observation was made that while evidence does not currently support concurrent 9 week treatment, further research may establish that a shorter period than 12 months treatment is actually the ideal regimen.

Some submitters noted that oncologists have advised patients that the evidence supports 12 month treatments. One submitter who had been diagnosed with HER2-positive breast cancer stated that her oncologist had advised her that with no treatment she would have a 10% chance of survival over ten years, with standard treatment (surgery, chemotherapy, radiation and hormone therapy) she would have a 40% chance of survival over ten years, but that if she also received additional 12 months Herceptin treatment, her chance of survival would double to 80%.

Evidence supporting that concurrent 9 week treatment is as effective as 12 months treatment

Some submitters thought that the evidence demonstrated that the concurrent 9 week treatment regimen with Herceptin was of comparable efficacy to 12 months treatment and that no evidence supported claims of any additional survival benefit of 12 months treatment over 9 weeks treatment. The comment was made that it was largely an accident of circumstance (because most of the clinical trials have used 12 months treatment) that the international oncology community views the 12 month treatment regimen as the “standard of care”.

The view was expressed that the results of the FinHER (concurrent 9 week treatment) trial were statistically significant and valid. One submitter considered that it would be irresponsible for any public funding body to ignore data from the FinHER study when considering the funding of Herceptin for HER2-positive early breast cancer.

The view was expressed that 9 weeks treatment may have some advantages over 12 months treatment in that shorter courses of treatment are more acceptable to patients and that under a shorter treatment regimen patients are less exposed to the toxicity of treatment, and are able to resume their normal lives sooner.

Finally, the view was expressed that there was good evidential and ethical grounds for funding the concurrent 9 week treatment with Herceptin and further investigating of the relative efficacy of concurrent 9 week treatment and 12 months treatment in a clinical study.

¹² St Gallen International Expert Consensus Guidelines, Goldhirsch et al., 2007

The evidence is not clear on the best treatment option

Some submitters noted that the available evidence does not clearly identify the best (in terms of relative efficacy and safety) treatment option for Herceptin in HER2-positive early breast cancer. The view was expressed that the key uncertainty is whether 12 month treatment regimens (sequential or concurrent) are any better than the comparator concurrent 9 week treatment regimen.

The point was made that although 12 months treatment is considered the standard of care internationally, the concurrent 9 week treatment has also been shown to have clinical benefit and it is not yet clear how the two treatment options compare.

Comments that further research is required to determine the best treatment option

Some submitters considered that important unanswered questions remain about the best duration and sequencing of Herceptin treatment, and specifically about how 12 months treatment compares to concurrent 9 week treatment. Some submitters considered that additional clinical trials are required to answer these questions.

One submitter considered that further 'unbiased' research into Herceptin should be undertaken and that those people who wanted 12 months Herceptin treatment now should pay for it.

The SOLD (9 weeks vs 12 months), PHARE (6 months vs 12 months), and PERSEPHONE (6 months vs 12 months) trials were identified as clinical trials that were being undertaken to explore questions of optimal duration of treatment, and it was noted that Roche (the supplier of Herceptin) is not involved in any of these trials. One submitter considered that the scientific community readily repeats trials that look promising and was puzzled as to why the FinHER trial was not being repeated until 2008. Another submitter commented that investigating the efficacy of a shorter duration of Herceptin treatment has not been a priority for the pharmaceutical industry.

Some submitters expressed concerns about the SOLD trial. In particular that patients are being effectively coerced into participation in SOLD by the 50:50 possibility of receiving the 12 months treatment considered to be the international standard of care. In addition, the view was expressed that SOLD patients are not receiving sufficient information in order to provide 'informed consent'.

It was noted that answers from the SOLD study would not be available for another seven years and considered that the wellbeing of New Zealand women should not be risked in the meantime [by only funding concurrent 9 weeks treatment].

The SOLD trial and PHARMAC's financial support of the SOLD trial was strongly supported by a number of submitters, with one noting that New Zealand was carrying out a vital international function in conducting the SOLD trial.

DHBs commented that they remained open to the receipt of new information about the relative benefits and costs of Herceptin compared with the currently funded concurrent 9 week treatment.

PHARMAC comments

A brief summary of the available clinical evidence for Herceptin in HER2-positive early breast cancer can be found in **Appendix 4** to this *Summary of Submissions* a more extensive summary of the available clinical evidence can be found on our website www.pharmac.govt.nz.

The currently available data for all Herceptin studies is relatively short term, with median follow-up of only 2-3 years. It is still too early to say for sure if Herceptin is a cure for HER2-positive early breast cancer or not. However, as the efficacy of Herceptin in most studies seems to be getting weaker over time, it is by no means assured that the early benefits seen with Herceptin will translate in the longer term to more 'lives' (years of life) being saved.

Although early data are promising, the benefits in terms overall survival at 2-3 years is relatively small, with an absolute survival improvement of 1.8%-2.9% for patients treated with Herceptin compared with those treated with chemotherapy alone (without Herceptin).

PHARMAC agrees with some submitters that the international view of 12 month treatment regimens being "standard of care" is largely by accident of circumstance (where most of the clinical trial work has been done with 12 month treatment schedules), and that the benefit a 12 month treatment, over shorter treatment, has not been proven.

The best treatment regimen for Herceptin in HER2-positive early breast cancer cannot be determined from the available evidence. More research is needed to address questions about the optimal treatment regimen (duration and sequence), hence PHARMAC's support for the SOLD trial.

On the basis of the evidence that is currently available, PHARMAC is not confident that there would be additional health gains to be made from funding a 12 month treatment regimen (concurrent or sequential) compared with the concurrent 9 week treatment regimen that is currently funded. On the basis of the indirect comparisons from the current trial evidence and the advice we have received from our clinical advisory committees, the Pharmacology and Therapeutics Advisory Committee (PTAC) and the Cancer Treatments Subcommittee of PTAC (CaTSoP), and following our own analysis of the evidence, we consider it reasonable to conclude that 12 months treatment may produce no additional health gain compared with the currently funded concurrent 9 week treatment regimen.

PTAC and CaTSoP concluded that the optimal treatment regimen for Herceptin (in terms of dosing, sequence, minimising cardiotoxicity and long term clinical benefits and risks) in HER2-positive early breast cancer cannot be determined from the current evidence. Only indirect comparisons of the various trials can be drawn. Those comparisons suggest that the funded concurrent 9 week regimen has comparable benefit in terms of disease-free survival as the various 12 month regimens (concurrent or sequential), although it is not currently possible to say whether the concurrent 9 week treatment regimen would result in overall survival benefits. Some of the 12 month treatment trials have demonstrated that disease-free survival gains are translated into overall survival benefits.

It is acknowledged that there is more confidence in the 12 month treatment trial results, and that the concurrent 9 week treatment (FinHER) trial data has not demonstrated a statistically significant benefit for overall survival, unlike some of the 12 month treatment trials.

However, although the FinHER trial was smaller, resulting in wider confidence intervals than the larger 12 month treatment studies, the results for disease free survival are statistically significant and the benefits shown are comparable to the 12 month treatment studies. PHARMAC, PTAC and CaTSoP have carefully considered these issues when evaluating the clinical evidence from the FinHER trial.

PTAC, having reviewed all the relevant data, specifically disagreed that the curves for the 12 months Herceptin trials mirror those of adjuvant chemotherapy. Increasing benefits of Herceptin over time (in terms of reducing hazard ratios for disease progression events) have not been demonstrated in any trials, maintained benefit has been seen in only one study (B31/N9831 concurrent arm), and some studies have shown a waning of benefit (HERA and BCIRG006) or no benefit over standard care (N9831 sequential arm and PACS04).

PHARMAC's view of the trial design and power of FinHER is discussed at length in the New Zealand Medical Journal (Appendix 4 to the June 2007 article, and August 2007 response¹³). Although the FinHER trial was smaller than the 12 month studies, resulting in wider confidence intervals on the results, the results for disease free survival were statistically significant (across the range of confidence) and the benefits shown were comparable to the 12 month studies with breast cancer disease recurrence more than halved. PHARMAC, PTAC and CaTSoP's evaluation of the clinical evidence from the all the trials, including the FinHER trial, has been rigorous.

It is not solely the size of the study that is all-important, but rather the interplay between the effect size (the difference in the number of patients experiencing disease recurrence in each arm) and the underlying patient group sizes. It is this interplay that gives the standard errors (and hence the width of the confidence intervals – i.e. precision around the results), and the relationship between group size and effect is not linear. With sufficient effect sizes (as occurs in FinHER) there can still be sufficiently robust results, statistically, even with small patient numbers.

The FinHER trialists estimated the study would be able to detect a 50-67% difference in HER2-positive patients' five-year recurrence-free survival (80% power) (Joensuu et al. New England Journal of Medicine (NEJM) 2006¹⁴). Any concerns around whether FinHER was sufficiently powered prospectively to assess sequential treatment are allayed by the trial's results; the statistically significant disease free survival result (Hazard Ratio 0.42, 95% confidence interval 0.21-0.83) means the study was indeed sufficiently powered to detect this difference. As few as 145 patients would have been needed for the results to still be statistically significant. The width of the confidence interval simply reflects the degree of precision, but does not invalidate results that are statistically significant.

The view that there is a 1:20 chance of the FinHER study result being false positive expressed by one submitter differs from the 1:100 estimate discussed by Hind et al in the Lancet 2007¹⁵ which observed: *"...improvement in disease-free survival in FinHER would be attributable to chance alone once in 100 times. The results of this trial are not as robust as those of HERA, but many treatments are funded with a lesser degree of certainty."* PHARMAC staff understand analysis in the Hind Lancet commentary supercedes the SchARR report (the source of the citation of 1:20) by the same authors.

Debates around the "certainty" of the evidence around Herceptin have related largely to the numbers of clinical trials and their patient numbers. There are, however, many factors that

¹³ 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>.
Isaacs RJ, Frampton CM, Kuper-Hummel MJJ. PHARMAC's funding of 9 weeks Herceptin: many assumptions in a high-risk decision. N Z Med J. 2007;120(1259). <http://www.nzma.org.nz/journal/120-1259/2676/>
Metcalfe S, Evans J. PHARMAC responds on Herceptin assumptions and decisions. N Z Med J. 2007 Aug 24;120(1260):U2692. <http://www.nzma.org.nz/journal/120-1260/2692/>

¹⁴ Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, et al; FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354:809-20. <http://content.nejm.org/cgi/content/full/354/8/809>

¹⁵ Hind D, Pilgrim H, Ward S. Questions about adjuvant Herceptin still remain. Lancet 2007; 369: 3-5. <http://www.thelancet.com/journals/lancet/article/PIIS014067360760004X/fulltext>

are important to assessing the robustness of the clinical data supporting treatments, of which numerical precision is only one. Bias for other reasons (beyond the play of chance) can just as easily give false results. It is therefore incorrect to differentiate evidence solely on trial size at the expense of other aspects of trial validity.

A statistically significant result is not necessarily of practical significance, or demonstrative of a large effect in the population. Given a sufficiently large sample, extremely small and non-relevant differences can be found to be statistically significant.

It has been observed that preoccupation with sample size overshadows the more pertinent concerns of elimination of bias, and that unbiased trials with imprecise results trump no results at all (Schulz and Grimes, Lancet 2005):

“Trials should be methodologically strong, thus eliminating bias. Unfortunately, the adequate-power mantra frequently overwhelms discussion on other methodological aspects, e.g. inadequate randomisation usually yields biased results which cannot be salvaged even if a huge sample size generates great precision. By contrast, if investigators design and implement a trial properly, that trial essentially yields an unbiased estimate of effect, even if it has lower power (and precision).”

FinHER was a well-conducted, properly randomised trial with good reporting and concealment of allocation. The baseline characteristics/prognostic indicators of the treatment groups were generally well balanced, with less favourable axillary nodal metastases and progesterone-negative tumours tending to be more frequent in the Herceptin treatment group.

Although there was criticism of FinHER by some parties, the 12 month trials Herceptin also have had serious issues affecting validity and these should also be acknowledged. For concurrent 12 months, the “weight of evidence” is hampered by the possible poorer quality of the relevant trials. This is where none of the three trials have published their individual results in order to allow due scientific scrutiny and peer review, and hence we cannot be confident of their methodological quality (yet where the FinHer trial was adequately reported):

- It is difficult to assess the quality of two of the three trials (B31 and N9831) because reporting has been limited to joint analyses. There has been virtually no disaggregation into the separate studies or any description of key validity aspects of the separate studies. Yet the two studies’ concurrent arm results for efficiency (but not cardiotoxicity, reported separately) have been published and presented as post-hoc pooled analyses limited to concurrent treatment groups that were of appreciably different design.¹⁶

For the other key trial concurrent 12 month treatment, BCIRG006, its results have limited to conference slideshow presentations, making it hard to assess validity.

Furthermore, most trials do not report their allocation concealment methodology, i.e. the efforts to ensure the study investigators did not know ahead of time which patients were assigned to what treatments. Such foreknowledge introduces bias by inappropriately assigning ‘winners’ to believed-superior treatments. Epidemiological convention is that

¹⁶ The N9831 and B31 trials of concurrent regimens in the Romond 2005 interim analysis differed in patient eligibility (high risk negative node status); methods of randomisation allocation; taxane regimens, anthracycline regimens, sequencing with radiotherapy, sequencing with hormonal therapy, aromatase inhibitor types, and when they started to be used in the trials; recommendations for post surgical radiotherapy; and primary endpoints (disease free survival (DFS) for N9831, overall survival for B31)

inadequate or unclear allocation concealment may mean 30-40% larger estimates of treatment effects than is truly the case¹⁷, which conceivably appreciably overstates results.

By contrast, FinHer is the only trial of all of the Herceptin trials that has published the results of all of its arms and has adequately reported its methods for concealing allocation.

In addition, criticisms that FinHER was an open-label study apply to all the 12 month Herceptin trials. The non-reporting of confounders such as socioeconomic status, smoking etc. equally applies to the other 12 month Herceptin trials.

Adding to uncertainty, with all of the Herceptin trials, only preliminary interim results have been reported. All the Herceptin trials continue to follow-up patients, and none have met their preset target event accruals. PTAC considers that the Herceptin data are subject to unacceptable publication bias, that data should have been published, and their continued absence raises important questions. PTAC has also restated that more clinical research is needed to see whether longer duration concurrent treatment is any better than short duration concurrent treatment, and the SOLD study may help answer this.

In terms of the lack of full study documentation for FinHER available for review, PTAC and CaTSoP have considered the FinHER data available to be of good quality and valuable. FinHER's NEJM publication (Joensuu et al. 2006) warrants that the trial investigators collected and maintained the data, and the authors vouched for the accuracy and completeness of the paper. The paper underwent NEJM's standard peer review process.

Regarding N9831 Arm B sequential data versus HERA data, the non-HERA 12 month sequential data (N9831 Arm B and PACS04) have an appreciable effect; combining data from all three 12 month sequential trials causes the central estimate of effect to reduce (28% risk reduction for the combined studies, compared with 36% reduction for the updated HERA data alone). Conversely, in the N9831 interim analysis 12 months sequential Herceptin was significantly less effective than 12 months concurrent therapy, increasing disease events by half (being the inverse of the concurrent vs. sequential HR of 0.64).¹⁸

PTAC considered that although data from the HERA study for sequential Herceptin treatment initially showed a similar treatment benefit to the concurrent studies, the improvements in disease-free survival for sequential Herceptin treatment in both PACS04 and NCCTG N9831 (sequential arm) were smaller and were not statistically significant, therefore data seemed to indicate that 12 months sequential treatment with Herceptin, per the MedSafe approved datasheet, may be a less effective use of the agent in treating HER2 positive early breast cancer patients.

Regarding PACS04, PTAC agreed with CaTSoP's view that criticisms of this trial are invalid. The study was adequately powered (80%) to detect a difference between treatment groups of 38%. CaTSoP considered that criticisms about the proportions of patients not receiving treatment or stopping treatment were invalid because the same situation applied to other Herceptin studies (e.g. in the combined B31/N9831 concurrent study 10% of patients failed to commence treatment and an additional 20% of patients did not complete more than 9 months of Herceptin therapy). CaTSoP considered that, despite the PACS04 study being smaller than some of the other 12 month Herceptin studies, the data were of good quality.

PHARMAC will be updating the Herceptin patient information leaflets with the available current evidence. We will also include information regarding confidence intervals in the

¹⁷ Schulz KF. Assessing allocation concealment and blinding in randomised controlled trials. Why bother? Evidence Based Medicine 2000; 5:36-37.

¹⁸ Metcalfe S, Carl Burgess C, Laking G, et al. Trastuzumab: possible publication bias. Lancet. 2008 May 17;371(9625):1644-6. <http://www.thelancet.com/journals/lancet/article/PIIS0140673608607060/fulltext>

patient information leaflet. The concept of 'confidence intervals' is difficult to describe in a patient information leaflet. PHARMAC does acknowledge that there is more confidence in the 12 month trial results, however, it is important to note though that although the FinHER trial was smaller, resulting in wider confidence intervals than the larger 12 month studies, the results for disease free survival are statistically significant and the benefits shown are comparable to the 12 month studies.

PHARMAC consider (as PTAC noted) that Herceptin data have been, and continue to be, subject to publication bias. The majority of international and national treatment guidelines do not take into account important unpublished data, including negative results from N9831 12 month sequential arm (Arm B) and the more recently presented PACS04 12 month trial. In addition they do not take into account the waning of benefit demonstrated in 12 months studies HERA or BCIRG006.

PHARMAC staff are not confident that there would be additional health gains from funding a 12 month regimen (concurrent or sequential) of Herceptin compared with the currently funded concurrent 9 week regimen. It is important to note that there are no head to head clinical data of 9 weeks' vs. 12 months' treatment; therefore at this point there is no evidence that 12 months' treatment is better than 9 weeks, or vice-versa. On the basis of the indirect comparisons from current trial evidence and the advice PHARMAC has received from PTAC and CaTSoP, PHARMAC think it is reasonable to assume that 12 month treatments may produce no additional health gain compared with the funded 9 week regimen.

Further research is needed to definitively answer the question of whether 12 months treatment is better than 9 weeks (or not), the SOLD clinical trial will address this question. CaTSoP considers that the SOLD study is well designed and will answer some of the questions relating to the optimal dose, duration and scheduling of Herceptin in early HER2 positive breast cancer. Prior to any patients being enrolled in the SOLD study, both the study protocol and the patient informed consent form must be approved by an Ethics Committee. The first patient was enrolled into the SOLD study on 4 January 2008 in Finland. As at 30 May 2008, internationally, 59 patients had been enrolled. Although no patients have been enrolled yet in New Zealand, four centres in New Zealand have Ethics Committee approval to conduct the study.

PHARMAC considers that investing additional funds in 12 months treatment with Herceptin, which cannot be determined from the current evidence to improve health outcomes compared with treatment with concurrent 9 week Herceptin, would not be a cost-effective use of resources.

Finally, in response to the advice by a submitter around survival estimates provided by her oncologist (10-year survival estimates for her of 10% for no treatment, 40% with standard treatment (surgery, chemotherapy, radiation and hormone therapy) and 80% with additional 12 months Herceptin treatment).

This information appears to have been derived from the Adjuvant!Online online database (<http://www.adjuvantonline.com/index.jspadjuvantonline>) regarding 10 year estimated survival, with manually applied extrapolation of short term (1-3 year) Herceptin data for disease-free survival to this information. In our view this is entirely inappropriate methodology and overstates the potential benefits of Herceptin for individual patients.

Anyone faced with information of this nature might feel compelled to find additional funding in order to privately receive a 12 month treatment regimen. We consider that it is essential that patients are provided with balanced material relating to the evidence, to assist them to understand the full set of data available for Herceptin to enable informed choices about

whether or not they wish to fund a different treatment regimen. To this end, PHARMAC is updating the Herceptin patient information leaflet with current evidence.

6. Cardiac side effects of Herceptin

Submitter's views

Submitters expressed differing views on the cardiac (heart) side-effects of Herceptin and how these weigh-up against the benefits of the different treatment regimens.

The view was expressed by oncologists that they rarely encounter the cardiac toxic side-effects of Herceptin treatment and that cardiac toxicity can be managed. It was noted that Nuclear Medicine MUGA scans for identifying cardiac toxicity are rapid and relatively inexpensive. The adverse cardiac effects Herceptin treatment were considered to be treatable and reversible when Herceptin is not administered concurrently with anthracyclines.

Some submitters considered that the benefits of 12 months Herceptin treatment regimen greatly outweighed the risks of cardiac toxicity. The view was expressed that funding for 12 months treatment should not be declined, because of the cardiotoxic side-effects, on the grounds of medical safety. The view was also expressed that individuals who have aggressive cancer accept that there may be risks as well as benefits associated with treatments. Others noted that the delayed [cardiac] side effects of Herceptin will take longer to confirm.

On the other hand, other submitters commented that the potential risk of cardiac damage outweighed the potential benefit of Herceptin. The comment was made that because many of the women in the target group to receive Herceptin treatment would have never died from their cancer [without Herceptin], the potential long term cardiotoxic effects of Herceptin cannot easily be dismissed. The view was also expressed that the adverse effects of Herceptin should be lessened by shorter exposure.

PHARMAC comments

The evidence demonstrates that Herceptin treatment is clearly associated with an increased risk of cardiotoxicity. PTAC considered that although cardiotoxicity appears to be manageable in the medium term with cessation of Herceptin treatment, some patients could still have sustained sufficient cardiac damage to require long term treatment for cardiac dysfunction and at times the initiation of other pharmaceutical treatment.

The long term benefits and risks (including cardiotoxicity and premature death from heart failure) are as yet unknown.

Some factors seem to predict worse cardiac outcomes in patients treated with Herceptin, including older age and prior administration of anthracycline chemotherapy. Importantly, both PTAC and CaTSoP consider that the assessment tools used for assessing cardiotoxicity in the clinical trials, i.e. measuring a decrease in left ventricular ejection fraction (LVEF), have poor sensitivity and therefore may not detect all clinically relevant cardiac harms from Herceptin treatment.

PTAC also considered that in clinical practice the incidence of Herceptin associated cardiotoxicity may be higher than that seen in the trials, due to less frequent monitoring and the treatment of patients with poorer baseline cardiac function.

7. The Cost-effectiveness and cost of Herceptin

Submitter's views

Submitters expressed a range of views relating to the assessment of the cost-effectiveness of Herceptin. These included that PHARMAC should repeat its cost-effectiveness analysis, that the costs of not providing treatment are outweighed by the costs of 12 months treatment, and, in opposition to this, that the additional costs of 12 months treatment are not justified. Some submitters also noted a new commercial proposal from Roche. Further detail on submitters' views is provided under the headings below.

PHARMAC should repeat its cost-effectiveness analysis

Some submitters suggested that PHARMAC should repeat its cost-utility analysis using new data that shows improved disease free and overall survival benefits after longer term follow up. These submitters considered that re-doing the analysis was necessary to determine the true net additional cost of increasing the level of funding from 9 weeks to 12 months.

The view was also expressed that recent data suggests the costs of treating metastatic HER2-positive breast cancer may have been underestimated by as much as three to nine times, and that the financial benefits of preventing disease progression by treating to cure in early stage disease have been significantly underestimated.

The costs of not providing 12 months treatment are greater than providing 12 months treatment

Some submitters were of the view that the 'costs' associated with not funding the 12 month Herceptin treatment regimen should be considered holistically, including psychological and psychosocial costs, and increased demand on health and disability services to support patients and their families. Some submitters considered that such costs were likely to far outweigh the cost of the funding 12 months treatment with Herceptin.

Some submitters considered that wider impacts on friends and family, the workforce and the economy - loss of women's contribution will impact on their contribution in work and in the home should be taken into account.

Roche's new 12 months funding proposal

The comment was made that Roche has presented a significant new funding proposal to PHARMAC and the submitters understood that this reduces the cost per quality adjusted life year (QALY) for the 12 months Herceptin treatment from \$29,436 to \$21,000 and reduces the overall cost to less than \$10 million per year.

The additional costs of 12 months Herceptin treatment is not justified

Some submitters made comments about the implications of funding 12 months treatment with Herceptin. Specifically, the view was expressed that the benefits of Herceptin are marginal and the costs of it are very high. It was also commented that 12 months funding came at an approximate cost of an additional £1.5 million per life saved (UK costs) and any

additional benefit comes at a high cost to other patients who are in need of healthcare. This submitter concluded that, in their view, at its licensed dose [12 months treatment] Herceptin could not be considered a priority for healthcare expenditure.

Some submitters considered the additional cost of funding 12 month's treatment could not be justified given the evidence of comparable effectiveness of the concurrent 9 weeks treatment and 12 month treatments. The comment was made that the projected additional cost of funding 12 months treatment with Herceptin would only be for the uncertain longer-term gain of a small number of patients. Another submitter expressed the view that any incremental gain in effect that would be achieved by extending treatment out to 12 months would be likely to be outweighed by the incremental cost. More evidence of the benefits of 9 weeks treatment compared with 12 months treatment was considered desirable to reduce the uncertainty in the data that this conclusion is based on. The view was expressed that the cost of funding 12 months treatment would be an unjustifiable and excessive cost for no additional survival gain over that which is currently indicated from the 9 week treatment regime. It was also expressed that the probability of the 9-week treatment regimen not being substantially more cost effective is very small whilst the cost effectiveness of year-long Herceptin is questionable.

A submission from a group representing cancer clinicians and DHB staff commented that, based on a total cost/cost benefit/health needs view, concurrent 9 weeks treatment is the most palatable situation for NZ at present, however they noted their opinion that the weight of clinical evidence sits with 12 months treatment.

A DHB commented that it does not have sufficient unallocated funds budgeted to be able to pay for 12 months Herceptin treatment.

It was also submitted that the PHARMAC proposal [not to fund 12 months Herceptin] is entirely appropriate, ethical and legitimate within a health care system with finite resources and with due regard to the economic status of the nation.

The view was also expressed that it is entirely appropriate that PHARMAC resists both public pressure and the private pharmaceutical companies' demands for scarce health dollars to be spent on what is very likely to turn out to be unnecessarily prolonged treatment periods with a vastly overpriced drug that carries an increased risk of adverse effects.

PHARMAC comments

PHARMAC undertook a new budget impact and cost-utility analysis (CUA) as part of its decision-making process (where budget impact and cost-effectiveness are two of PHARMAC's nine decision criteria). The cost-utility analyses are based on consistent CUA policies and methodology, as outlined in PHARMAC's Prescription for Pharmacoeconomic Analysis (PFPA)¹⁹, including measuring all health sector costs and health related quality of life and/or life expectancy.

Cost-utility analysis is considered the gold-standard for the analysis of health intervention and is used by most international assessment agencies. CUAs include information on both the additional net costs to the health sector of a funding decision (e.g. cost to the hospital of administering treatment, savings from reduced relapses) and the additional health gain (e.g. increased survival, improved health-related quality of life). This information is combined to obtain an overall cost per quality-adjusted life year (QALY) estimate, which can be compared

¹⁹ <http://www.pharmac.govt.nz/2007/06/19/PFPAFinal.pdf>

with other treatments for other diseases to determine which interventions provide the maximum health gains from the budget available.

Note that a CUA is based on the incremental cost and gains of treatment – i.e. the difference in costs and quality-adjusted life year gains between the new treatment compared with currently funded treatments. PHARMAC's analyses include all costs and cost offsets are for the health care system as a whole and measured long-term, not just short-term pharmaceutical costs. Health related quality of life measures inherently encompass psychological/psychosocial aspects. In the case of Herceptin, the costs of terminal care and lower quality of life associated with terminal cancer (including the psychological aspects of terminal cancer) were included in the analysis, as Herceptin treatment is likely to delay the time when terminal care is required.

PHARMAC has updated the cost effectiveness modelling for Herceptin since its previous decision in April 2007 to fund the concurrent 9 weeks treatment. Relevant concerns raised in consultation submissions have been either included in the model or tested in the sensitivity analyses (e.g. higher costs associated with the treatment of metastatic breast cancer). The new evidence, assumptions, methods and results of the analysis are documented in Further Supplementary TAR (Technology Assessment Report) 75c which is posted on our website at www.pharmac.govt.nz.

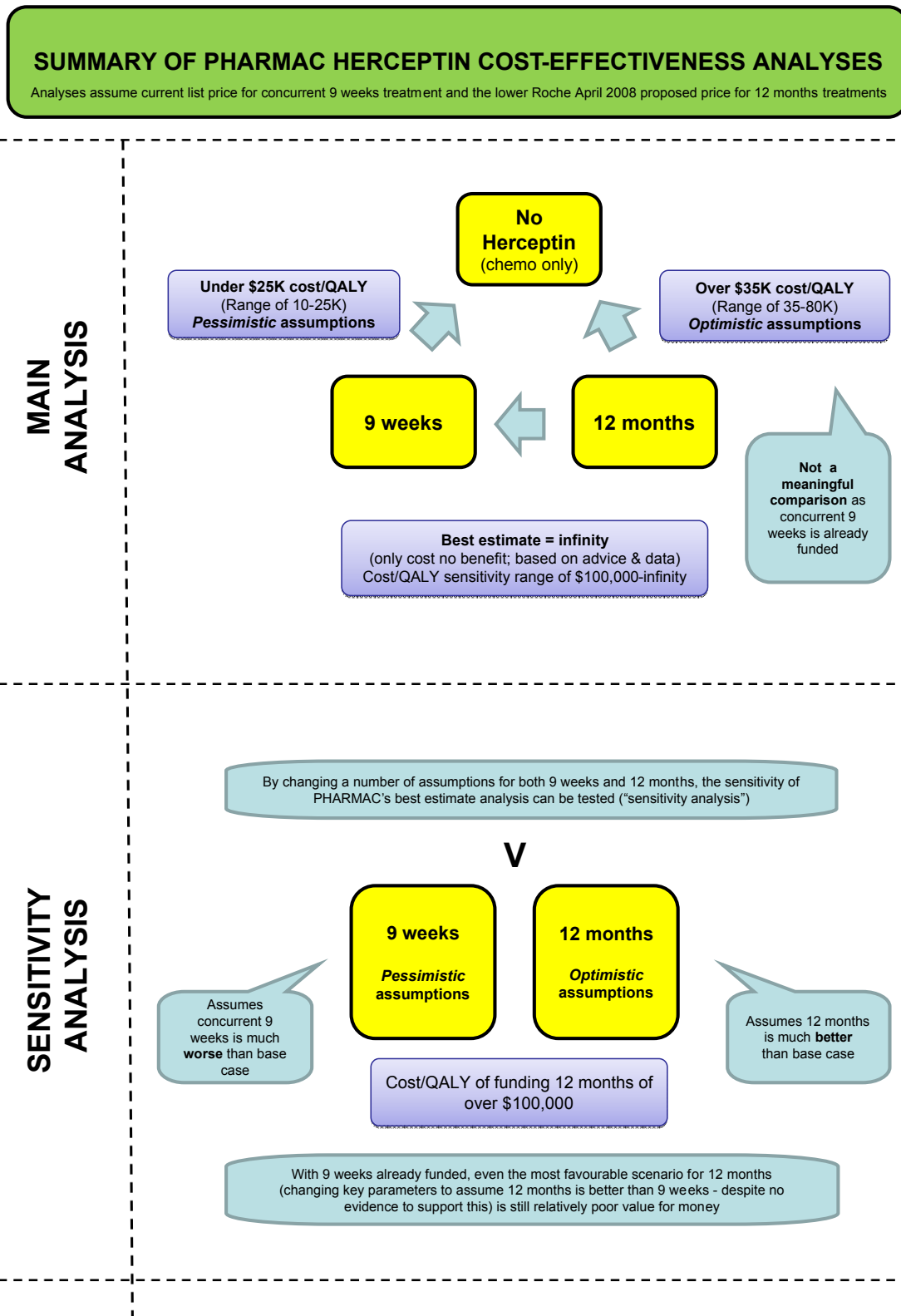
PHARMAC has compared the cost effectiveness of 12 months concurrent/sequential treatment, concurrent 9 week treatment and standard care (i.e. chemotherapy only, no Herceptin). The Herceptin CUA models the incremental costs and benefits over the lifetime of the patient population, therefore includes both the short and long-term costs and benefits of treatment.

The base case results of this analysis indicate that the concurrent 9 week treatment regimen dominates the 12 month treatment regimens (i.e. produces on average the same, or greater, benefits at a lower cost). Given the uncertainty surrounding the benefits of Herceptin for this indication, additional sensitivity analyses were undertaken. Sensitivity analysis of the cost-effectiveness of the concurrent 9 week treatment Herceptin regimen compared with standard care (chemotherapy only, no Herceptin) confirmed that this regimen is relatively cost-effective (compared with other treatments that could have been funded at the time). With sensitivity analysis using pessimistic assumptions regarding the efficacy and duration of effect for the 9 weeks treatment regimen, the cost-effectiveness remains in the range of 40-100 QALYs gained per \$1 million invested (\$10,000-\$25,000 per QALY).

The main sensitivity analysis assumed that the expected benefits of concurrent 9 week Herceptin treatment to be lower than the expected benefits from the concurrent 12 months treatment regimen. This scenario assumes the relative risk (RR) of disease recurrence with the concurrent 9 weeks treatment regimen to be only as effective as concurrent 12 months treatment, and much greater waning of treatment effect (shorter duration of treatment benefit) for concurrent 9 weeks treatment compared with the concurrent 12 months treatment regimen. These assumptions disfavour the concurrent 9 week treatment regimen compared with the concurrent 12 months treatment regimen. In this sensitivity analysis, the cost-effectiveness of concurrent 12 months treatment compared with concurrent 9 week treatment is less than 10 QALYs per \$1 million invested (incremental cost per QALY over \$100,000).

In this assessment we also included a scenario in which the concurrent 9 week treatment is assumed to have no benefit (or not to exist) and 12 month concurrent treatment is assumed to have an extended and durable benefit (neither scenario being currently supported by the evidence), using the net costs from the commercial offer from Roche, 12 months concurrent treatment with Herceptin under this scenario could at best generate 20-28 QALY's gained per million (a cost per QALY of \$35,000-\$50,000). Even if this situation was true, it would be difficult to justify funding a 12 month regimen on the grounds of cost-effectiveness given the

other opportunities that we currently have for funding pharmaceuticals. The above features can be seen in the following summary diagram:



PHARMAC has assessed the incremental budgetary impact of the 'bundled' commercial offer from Roche taking into account the current funding of 9 weeks treatment with Herceptin and funding already allocated for the SOLD study. Roche's offer was provided to PHARMAC on a "commercial in confidence" basis therefore PHARMAC will not breach that confidence, despite widespread commentary about some aspects of the proposal that have been released publicly (and portrayed as true). PHARMAC analysis of the incremental cost to DHBs (i.e. cost on top of funding already funded 9 week treatment regimen and the cost of funding the SOLD trial) of Roche's proposal is much higher than the 'less the \$10 million dollars" per year cited by some submitters. PHARMAC's assessment of the incremental cost (over and above funding already allocated for concurrent 9 weeks Herceptin and the SOLD study) of Roche's 'bundled' commercial offer for Herceptin and one other product is that it would be at least \$9 million per annum initially in the first 4 years, increasing to \$17-19 million annually once enrolment into the SOLD study had been completed.

8. Legal issues

Submitter's views

A few submitters made allegations of breaches of the law by PHARMAC. One submitter alleged that PHARMAC's conduct amounts to a 'malfeasance of justice' in that we have made media releases informing that PHARMAC is funding Herceptin for HER2 positive patients withholding the fact that the funding is for a regime of only "14.5% of the Internationaly [*sic*] accepted standard of 18x3 weekly infusions over 52 weeks". The same submitter expressed concern that the making of a submission could, in itself, breach the "Electoral Law Reform Act".

Two submitters made allegations that PHARMAC's actions amount to breaches of the New Zealand Bill of Rights Act 1990 (**NZBORA**); in particular of section 8 (Right to Life) in relation to the 9 week funding decisions and section 10 (Informed Consent) in relation to the 9 week funding decision and to the SOLD study. Another submitter made similar allegations although they were made with reference to the Cartwright Inquiry from the late 1980s and not specifically to the NZBORA.

One submitter expressed the view that PHARMAC is breaching its Treaty of Waitangi obligations.

PHARMAC comments

PHARMAC took these allegations seriously however, in our view, none of the allegations made can be substantiated.

9. The impact of HER2-positive breast cancer on women, their families and friends

Submitter's views

Many submitters described the emotional stress that accompanies a diagnosis of HER2-positive cancer, in addition to the negative physical effects of the disease and side-effects of Herceptin treatment.

Some submitters expressed the view that raising money – whether through extending mortgages, selling property, fund-raising, or continuing to work when feeling very unwell – added an unnecessary and significant burden to the difficulties associated with managing the disease. It was submitted that the cost of Herceptin is beyond the capability of many families. It was submitted that women with HER2-positive cancer were prioritising fund-raising and campaigning activities over other more meaningful and rewarding activities such as spending time with friends and family, and getting well. The view was also expressed that the impact on patients of not funding the [12 month] treatment recommended their oncologists is immense and not in keeping with the objectives of the Medicines Strategy.

It was also suggested PHARMAC's decision not to fund 12 months created inequities based on financial circumstances. Further this was considered to be unfair because, it was commented that New Zealanders expect equal access to medicines for all.

The view was expressed that New Zealand women who are living overseas when diagnosed with HER2-positive breast cancer would prefer to return to New Zealand to benefit from the support of friends and family when receiving treatment. It was submitted that currently these women have to make a choice between receiving the optimal treatment and being closer to family.

Many submitters shared their experiences of the loss of a relative – be it a mother, sister, wife or daughter – and noted that it has a big impact on a family and can lead to family breakdown. It was considered particularly important by some submitters that mothers of dependent children receive treatment so that they could continue to take care of them.

Many submitters asserted the importance of doing everything possible to support New Zealand women and extend their lives as long as possible.

PHARMAC comments

We acknowledge the considerable difficulties – emotional stress, uncertainty and worry – that family, friends, communities and the patient experience following a diagnosis of HER2-positive breast cancer.

Herceptin is currently fully funded for HER2-positive advanced/metastatic breast cancer, and specifically the concurrent 9 week Herceptin treatment regimen is effective and is available, fully funded, for all women with HER2-positive early breast cancer.

Our view is that private funding of 12 months treatment is an individual's choice. However, we do acknowledge the additional stress that this choice may cause.

We are concerned that the women who choose to privately fund 12 months treatment do so because they believe that the publicly-funded concurrent 9 week treatment regimen is not effective. In our view there is no evidence to show that 12 months treatment regimen offers any additional benefit over the funded concurrent 9 week treatment.

PHARMAC consider that it is essential that patients be provided with balanced material about the funding decision for the 9 week treatment regimen as well as information about the 12 month treatment regimen. This is critical to assist patients to understand the full set of data available for Herceptin in order that they can make an informed choice about whether or not to self fund 12 months Herceptin treatment. To this end PHARMAC will be updating its Herceptin patient information leaflet which can be found on our website.

Other broader themes related to the New Zealand Medicines funding framework

10. International comparisons

Submitters' views

Some submitters compared aspects of New Zealand's pharmaceutical funding system, approach to funding Herceptin, and outcomes for patients with breast cancer, to those of other countries.

Specifically, the view was expressed that New Zealand's pharmaceutical expenditure is too low at only 6% of the health budget, compared to Australia's 12%. The comment was also made that since PHARMAC's formation in 1993, the pharmaceutical spend has decreased from 11% of the health budget to less than 6% in 2006, and that the OECD average is currently 18%. One submitter included a statement that New Zealand women with breast cancer are 33% more likely to die from the disease than Australian women.

Some submitters expressed the view that New Zealand with is out-of-step with other OECD countries by not funding 12 months Herceptin treatment. The comment was also made that international treatment guidelines recommend the 12 month treatment regimen. In their submissions some parties cited various international clinical treatment guidelines, (including the St Gallen Expert Consensus Report 2007, the 2005 UK NCRI Breast Cancer Study group guidelines and the 2007 Australian National Breast centre recommendations) as being supportive of the 12 month treatment regimen (concurrent or sequential) and unsupportive of the 9 week FinHER treatment regimen.

On the other hand, a submission from a group of UK public health doctors and other health practitioners expressed the view that the New Zealand public should understand that PHARMAC is not alone in its view that the 9 week treatment regimen, not the 12 month treatment regimen, should be funded. They welcomed the fact that one country, at least, has had the courage to pursue what many consider to be the optimum policy option and commented that if they had been able to choose, most Primary Care Trusts in England would not have supported funding 12 months treatment with Herceptin and would have looked to fund a 9 week treatment regimen in some form instead. This group attributed the reason for the difference in PHARMAC's decision (to fund 9 weeks treatment) and NICE's decision to (recommend 12 months treatment) to NICE's restricted remit which does not include analysis of questions of affordability. The group also noted that NICE cannot take into account or recommend non-licensed pharmaceuticals or indication and cannot take opportunity cost into account.

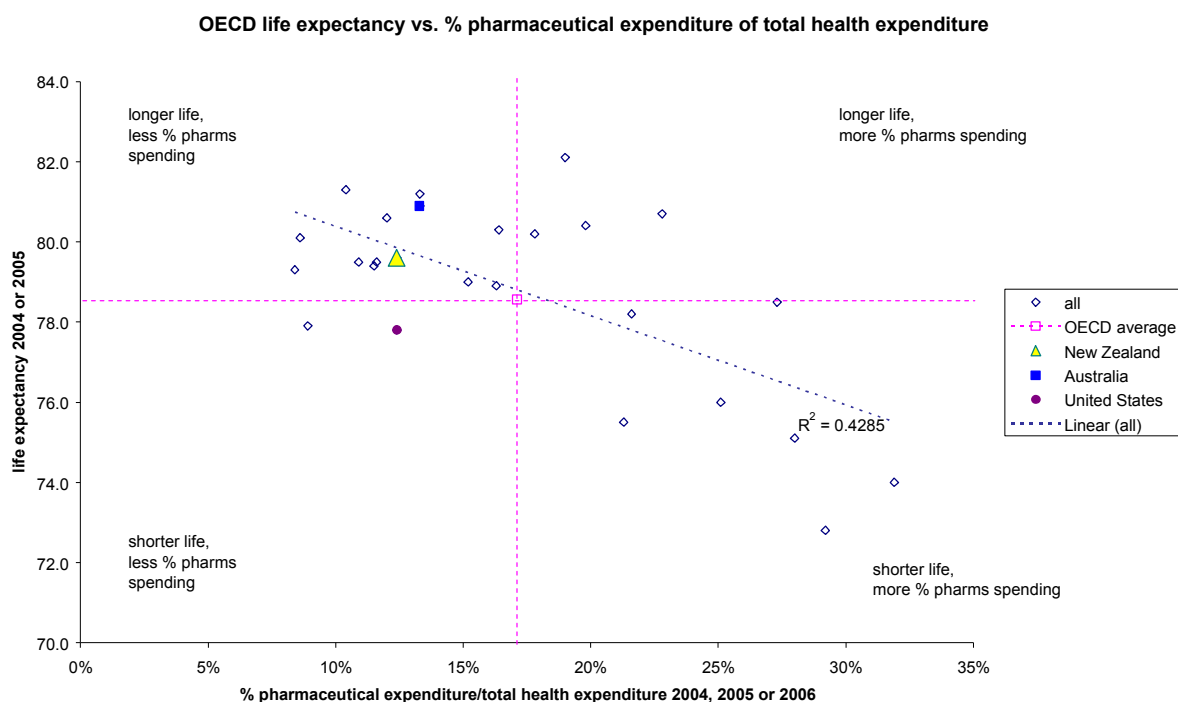
PHARMAC comments

With regard to comments on the size of the pharmaceutical budget, drawing reliable conclusions from international comparisons of spend on pharmaceuticals is very difficult due to a wide range of relevant factors that are different in each country. Simple metrics, like spending as a percentage of GDP, take no account of a range of factors across countries, such as relative health outcomes for that expenditure, different pharmaceutical purchasing models, different price movements in pharmaceuticals, different country wealth levels, and different national priorities and choices. We are unsure of the source of the 6% figure stated

by one submitter. According to the relevant table in the OECD data²⁰, pharmaceutical expenditure comprised 12.4% of New Zealand's total expenditure on health in the year 2006 – notwithstanding the above likelihood that New Zealand's hospital pharmaceuticals are not fully captured by these data, whereas they may be elsewhere.

Furthermore, the 6% figure quoted by submitters will not include all spending on hospital pharmaceuticals, much spending of which is not captured at all well by current information systems. For example, ~\$16.9 million is spent each year via the Pharmaceutical Schedule for cancer medicines (excluding endocrine treatments) dispensed in the community (by and large), but the spending on the overall Oncology Basket (all cancer medicines, whether used in hospital, outpatient settings or dispensed/used in the community) is perhaps an additional \$50-60 million. By contrast, the OECD data do capture hospital pharmaceuticals costs in other countries²¹. Hence the New Zealand figure is artificially low compared with other countries.

Any (exaggerated) "low" percentage of pharmaceuticals to total spending in New Zealand does not necessarily relate that well to more objective measures of system performance, where for example New Zealand has lower than average percentage but higher than average life expectancy. In fact the OECD data arguably suggest there is a good *negative* correlation between percentage pharmaceutical/total health spending and life expectancy in the OECD – the higher the percentage, the worse the life expectancy (R^2 0.42), as suggested in the following graph.



PHARMAC staff have been unable to verify a submitter's statement that New Zealand women with breast cancer are 33% more likely to die from the disease than Australian women from the source data cited by that submitter (<http://www.aihw.gov.au/publications/can/bca06/bca06.pdf>), nor have analysed other likely contributory factors such as comparative breast screening rates etc. The AIHW report indicates that New Zealand has the same age-standardised mortality rate for breast cancer as the UK. There is no stratification by HER2 status, and the Australian data do not extend

²⁰ <http://www.oecd.org/dataoecd/46/36/38979632.xls>

²¹ <http://www.ecosante.org/index2.php?base=OCDE&langh=ENG&langs=ENG>

beyond 2002, which predates the Australian Pharmaceutical Benefits Scheme (PBS) 1 October 2006 funding of Herceptin for HER2-positive early breast cancer. Clearly the funding, or not, of Herceptin is not a factor contributing to the identified disparity in breast cancer mortality. Even if Herceptin funding was a contributing factor to the disparity noted, PHARMAC consider there is currently no evidence that funding for 12 months treatment would provide any additional health benefits, or reduce disparities any better, than funding for concurrent 9 weeks treatment.

In our view, the fact that many other OECD countries fund 12 months Herceptin treatment is not in itself a reason for New Zealand to take the same approach. Different countries have different healthcare environments and decision-making frameworks. We need to make good decisions in the New Zealand context in accordance with our statutory objective, which is "*to secure for people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided.*" Our role is to make funding decisions that are in the best interests of New Zealand; this means making our own robust decisions independently of other countries.

Some countries that fund Herceptin for 12 months treatment have made this decision without evaluating the benefits, risks and cost effectiveness of treatment, others countries have capped funding mechanisms or 'fund' only where patients have their own private health coverage.

With respect to submitters' comments about international guidelines that support 12 months Herceptin treatment, we note that some of these also recognise that there are unanswered questions about the optimal regimen and that a short duration treatment (9 weeks) is also effective. PHARMAC note that aside from the sections of international guidelines cited by submitters as being unresponsive to 9 weeks Herceptin treatment, the Australian National Breast centre recommendations give the 9 week FinHER data the same ranking for level of evidence (level II) as the HERA, NCCTG-N9831 and NSABP-B31 studies, and noted there several unanswered questions including: the optimal duration of adjuvant Herceptin with chemotherapy; the long term effects of cardiotoxicity; and the long term benefits of Herceptin. The UK NCRI guidelines state that FinHER '*suggests that short duration (9 week) Herceptin...may also be very effective. This needs further investigation in a larger trial.*'

It is also noted that, generally, the international clinical treatment guidelines have excluded consideration of some relevant important unpublished information including negative data from the N9831 Arm B and PACS04 clinical trials, although some did consider unpublished follow-up data for combined studies N9831/B31 and BCIRG006. All of these data are important and should have been considered.

11. Government prioritisation of health spending and pharmaceutical costs

Submitter's views

Submitter's made a range of points about the resources that are available for spending on health versus other Government priorities, on the challenges posed by new expensive medicines, and on the size of PHARMAC's medicines budget.

Specifically the view was expressed that the public health system in NZ has been under-funded for so many years now that some New Zealanders are experiencing almost third world health care. The comment was also made that the Government should prioritise funding for 12 months' treatment with Herceptin over other areas of spending such as stadiums, and funding for prisons and the rehabilitation of criminals. It was further

commented that the money is available to fund 12 months treatment as the Government has been operating huge surpluses. Many submitters commented on expecting to benefit from the taxes they pay. One submitter said they'd be happy not to have tax cuts so the money could pay for Herceptin. Another submitter noted that the NZ government spends millions of money on road safety and not half as many people die from breast cancer as die on our roads.

Some submitters considered that it was PHARMAC's role to lobby for a greater medicines funding budget and that it had been incompetent for not doing this successfully.

The view was expressed that the costs of many new treatments have increased dramatically in the last 10 years and that funding these will be a challenge for even the most affluent of countries. One submitter commented that Herceptin is the tip of the iceberg. The comment was also made that health communities needed the freedom to explore alternative solutions, such as funding for 9 weeks treatment with Herceptin, to make good but unaffordable treatments available.

PHARMAC comments

With respect to comments about how Government funding would best be used, it is not PHARMAC's role to determine the priority of funding 12 months' treatment with Herceptin, or of pharmaceuticals generally, relative to other Government spending priorities.

In addition, if sufficient funding was made available to PHARMAC to cover the additional cost of 12 months Herceptin treatment, there are current applications for funding for other pharmaceuticals that would likely generate greater health gains for the money spent (including in the area of cancer treatment).

We agree that there are a number of new high cost treatments, particularly in the area of cancer. We therefore need to continue to make careful choices about which medicines to invest in, and how. The funding of these is an international challenge, not just a problem for New Zealand. Because money is limited in any setting, choices will always have to be made regardless of the size of the budget. The wider question is how we (society) make those choices. A European report published earlier this year estimated that if all new cancer medicines coming on line were to be funded in the UK, base rate taxation would need to rise to 60% to pay for them (http://www.euro.who.int/observatory/Publications/2007/20080204_1).

In response to comments about PHARMAC's role in increasing the size of the budget, the funding for 12 months Herceptin treatment would need to come from District Health Boards' budgets and not the Community Pharmaceuticals Budget.

PHARMAC forecasts the anticipated amount of funding required in the Community Pharmaceuticals Budget, given its view on any changes to the forecast of currently funded medicines and the likelihood of any current applications being justifiable for funding in the coming year. PHARMAC then consults with DHBs on their views about an appropriate budget figure (after sharing its forecast analysis with them). PHARMAC's notional Community Pharmaceuticals Budget is set by the Minister of Health on the basis of advice from PHARMAC and DHBs.

12. PHARMAC's funding processes

Submitter's views

The view was expressed that there are limitations on the pharmaceutical budget, and that prioritisation on the basis of an agreed set of principles is required, as not all medicines can be funded. In addition it was commented that high-cost medicines should be assessed using the same process that applies to other treatments.

The comment was made that in the interests of transparency, the decision making process should be separated into 3 areas: clinical safety and efficacy; cost benefit analysis, and the funding decision.

Some submitters' questioned PHARMAC's prioritisation of treatments for funding. The view was expressed that PHARMAC should spend more money on fatal diseases such as cancer (including by funding 12 months Herceptin), compared with other 'lifestyle' diseases like type 2 diabetes and stomach upsets. The question was also asked why only \$16.6 million is spent on cancer drugs compared with \$75.5 million on drugs to treat stomach upsets.

The comment was made that PHARMAC should not under-spend its budget each year, as this money could be used to fund 12 months Herceptin.

PHARMAC comments

With respect to the comments raised about transparency, these matters were considered in detail in the Government's recent work on developing a medicines strategy. The outcome of that strategy work, *Medicines New Zealand*, found that – while improvements were necessary – current structures are sound. Our view is that clinical, economic and commercial factors are best considered together, as they are all interdependent in terms of making sound funding decisions.

If cancer treatments, or other treatments for fatal diseases, provide good benefits for the cost compared to other treatment options awaiting funding, then they would likely be funded (after considering all nine of PHARMAC's decision criteria). Similarly if treatments for type 2 diabetes, heart disease, stomach ulcers and other so-called 'lifestyle conditions' provide good benefits for the cost compared to other treatment options awaiting funding, then they would be likely be funded.

In 2006 \$16.6 million of the Community Pharmaceuticals Budget was spent on cancer medications, and an additional approximately \$50 million was spend on cancer medicines delivered in DHB hospitals. We note that PHARMAC spending of \$75 million on antiulcerants as set out in our Annual Review does not take into account rebates for these medicines. The actual spend on antiulcerants is considerably lower, because the supplier of one of the most prescribed products pays PHARMAC a rebate of around 80% of total expenditure. A number of the rebates that PHARMAC negotiates are confidential, therefore PHARMAC expresses all expenditure in 'before rebates' terms in its Annual Review. PHARMAC staff realise that this can cause confusion and will keep this in mind in the future.

PHARMAC is a Crown Entity responsible to the Minister of Health and which (in effect) acts as an agent for District Health Boards (DHBs). PHARMAC's notional community pharmaceuticals budget is set each year by the Minister of Health following discussion with PHARMAC and the DHBs. As part of this process PHARMAC forecasts the anticipated

amount of funding required, given its view on any changes to the forecast of currently funded medicines and the likelihood of any current applications being justifiable for funding in the coming year. Any underspend is retained by DHBs to spend on other healthcare interventions.

13. The role of the Media

Submitter's views

The view was expressed that the mainstream media ignore commercial influences by continuously referring to a “twelve month gold standard” when advocating for public funding. It was commented that the general public generally trusts that “a gold standard” in the clinical medicine context refers to evidence based practice, yet the 12 month treatment regime was led by the drug company producer and established from a commercial decision basis.

One submitter noted that the current disproportionate emphasis of many to the use of Herceptin is putting the lives of sufferers in danger [from unnecessary side effects] and they support efforts to correct that overemphasis. Another submitter noted that they were very concerned about the public image of HER2-positive breast cancer as an always deadly disease and the promotion of Herceptin as an early breast cancer cure, as this is not supported by the evidence. They were particularly concerned by the manipulation of women with breast cancer to endorse, support and demand Herceptin. This submitter also had concerns about publication bias in Herceptin clinical trials.

PHARMAC comments

We consider that some media coverage has been uncritical of the Herceptin evidence and taken sometimes inaccurate statements by commentators as factual. As a result, some coverage has been unbalanced. For example, some media reports report 12 month treatments as the ‘gold standard’ with associated implications that the funded concurrent 9 week treatment is substandard or only part funding. Phrases such as ‘the full 12 months treatment’ are routinely used by the media and advocacy groups. There is also often an implication that, because HER2-positive breast cancer is a more aggressive form of the disease, women who do not receive trastuzumab, in particular the ‘full 12 month treatment’, are facing a death sentence. The evidence does not support this position.

PHARMAC is concerned that there is undue pressure on women, their families and communities to feel compelled to find additional funding in order to receive 12 months treatment.

PHARMAC considers that it is essential that patients be provided with material that is balanced, including that supporting the concurrent 9 week treatment regimen, to assist them to understand the full set of data available for trastuzumab and in turn to enable them to make an informed choice about whether or not they wish to fund addition trastuzumab treatment beyond the currently funded concurrent 9 week regimen.

This is not an issue unique to New Zealand. We note two papers published in the Journal of the Royal Society of Medicine examining media coverage of Herceptin (coverage in UK print media²², Australian television²³). The studies found that overall the media coverage was

²² Wilson PM, Booth AM, Eastwood A, Watt IS. Deconstructing media coverage of trastuzumab (Herceptin): an analysis of national newspaper coverage. J R Soc Med. 2008 Mar;101(3):125-32. <http://jrsm.rsmjournals.com/cgi/reprint/101/3/125>

uncritical and presented mainly emotional arguments, and did not adequately examine wider questions around costs to society among others. Media did not routinely report or question the motivations of those reported. In the case of the Australian study, the authors comment that, in taking that perspective, the news media would likely make poor choices for society overall (being emotionally-driven). The paper also suggests that the media coverage may have created an environment that indirectly influenced Australia's PBS and Government to make a funding decision that it had previously rejected on three occasions.

Where particularly unbalanced items have occurred in NZ media, PHARMAC has taken direct action, including the successful complaint against TV3 for its Herceptin 60 Minutes documentary of October 2006. The Broadcasting Standards Authority (BSA) found the documentary breached the BSA code of practice on three counts – one of overall balance and two of inaccuracy.²⁴

²³ Mackenzie R, Chapman S, Salkeld G, Holding S. Media influence on Herceptin subsidization in Australia: application of the rule of rescue? J R Soc Med. 2008 Jun;101(6):305-12. <http://jrsm.rsmjournals.com/cgi/reprint/101/6/305>

²⁴ Broadcasting Standards Authority 2006-127. CanWest TVWorks and Pharmac. 60 Minutes. Funding of herceptin. Balance, accuracy. Upheld. <http://www.bsa.govt.nz/decisions/2006/2006-127.htm>

APPENDIX 1: CONSULTATION LETTER

5 May 2008

Proposal regarding the funding of 12 months treatment with Herceptin (trastuzumab) for HER 2 positive early breast cancer

Overview

Recently the High Court ruled on a Judicial Review of PHARMAC's processes surrounding its decisions to fund a 9 week concurrent treatment regimen of Herceptin (trastuzumab) for HER 2 positive early breast cancer patients, and not to fund a 12 month treatment regimen.

The Court found that in July 2006 PHARMAC should have consulted prior to its decision to decline Roche's application for funding for 12 months treatment with Herceptin, administered following completion of chemotherapy (12 months sequential treatment). The Court set the decision aside and directed PHARMAC to make a new decision regarding Roche's application, following consultation.

The PHARMAC decision to fund 9 weeks treatment with Herceptin administered concurrently with chemotherapy ("9 weeks concurrent treatment") remains in place for New Zealand women to access and this proposal, to decline the funding of 12 months treatment with Herceptin, would not have any impact on the funding for 9 weeks concurrent treatment.

Proposal

We are now seeking comment and additional information on a proposal to decline the funding of 12 months treatment with Herceptin for HER 2 positive early breast cancer.

If the PHARMAC Board approve this proposal it would mean that Roche's application for funding of 12 months sequential treatment with Herceptin, and other proposals relating to the funding of 12 months concurrent treatment with Herceptin, would be declined. PHARMAC would no longer be actively working on any proposal regarding the funding of Herceptin in early breast cancer.

Should information change regarding the relative benefits and costs of Herceptin compared with the currently funded 9 weeks concurrent treatment, PHARMAC would remain open to considering further applications for funding. Any future decisions would then consider the relative merits compared with other funding options available at the time.

Nature of consultation

We consider that good consultation is best achieved through clarity about our proposal for funding applications. This approach ensures PHARMAC is transparent about its current thinking, and enables affected parties to provide meaningful responses on how the proposed decisions may impact on them. This does not mean that a decision has already been made. Rather, it reflects the view we have reached on the basis of available information. This view may change as a result of the information PHARMAC receives through consultation. In this instance, PHARMAC's proposal is to decline funding. PHARMAC will, of course, take into account all information received in consultation when reaching a decision on 12 months treatment with Herceptin for HER 2 positive early breast cancer.

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PHARMAC welcomes any and all views on this proposal. PHARMAC's role is not to 'count votes' but rather to ensure that it considers all relevant information in front of it about the potential effects, before reaching a decision.

Comments sought

We would welcome any comment you have on this proposal. To assist PHARMAC's consideration of submissions, submitters are encouraged to provide reasons supporting their views.

In particular comment regarding the comparative risks and benefits between 9 weeks and 12 months (sequential or concurrent) treatment regimens would be helpful. This would assist PHARMAC in considering the merit of investing in extra resources that 12 months (sequential or concurrent) treatment would require, when considering the proposal against its Decision Criteria.

In deciding which medicines to fund, PHARMAC seeks to balance the needs of patients' access to healthcare against its responsibilities to the taxpayer. Given PHARMAC is managing taxpayer funding, PHARMAC's decisions need to represent good value for money for the benefit of all New Zealanders. When considering which medicines to fund PHARMAC therefore takes into account a range of Decision Criteria including:

1. The health needs of all eligible people;
2. The particular health needs of Maori and Pacific peoples;
3. The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;
4. The clinical benefits and risks of pharmaceuticals;
5. The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;
6. The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Schedule;
7. The direct cost to health service users;
8. The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere; and
9. Such other criteria as PHARMAC thinks fit.

To provide comment please submit an email, fax or letter by **5 pm, Monday 9th June 2008** to:

Jackie Evans
Therapeutic Group Manager
PHARMAC
PO Box 10-254
Wellington 6143

Email: jackie.evans@pharmac.govt.nz

Fax: (04) 460 4995

If you require further information about this proposal you can contact Jackie Evans at jackie.evans@pharmac.govt.nz or (04) 916-7557.

All comment and additional information received before the closing date will be considered by PHARMAC's Board prior to making a decision on this proposal.

Our view in July 2006 was that funding 12 months' Herceptin could not be justified under our decision criteria. Since then some new information has become available. However, our preliminary view is that this new information would not have a material impact on this proposal since the last consideration of this matter by our Pharmacology and Therapeutics Advisory Committee (PTAC). Therefore we have decided to issue this proposal with speed as directed by the Court, and without seeking further advice from PTAC at this time. This and any other new information, along with consultation responses, will be taken into account before any decision is made

We anticipate that a decision would be made in June. However, if new information comes to light as a result of this consultation or as a result of presentation of new material (e.g at the American Society of Clinical Oncology conference in May/June) we will consider whether a delay is needed for further assessment and advice before making a decision.

Background

PHARMAC received an application from Roche for funding 12 months sequential treatment with Herceptin in December 2005. By July 2006 PHARMAC was not in a position to recommend funding of Herceptin, and made a decision at that time to decline funding, pending further review.

PHARMAC decided, after considering advice from the Pharmacology and Therapeutics Advisory Committee (PTAC) and its cancer treatments subcommittee, in April 2007 that under its Decision Criteria funding 9 weeks concurrent treatment with Herceptin was a good use of the funding available compared with other uses, and approved funding on this basis.

Recently the High Court ruled on a Judicial Review of PHARMAC's processes surrounding its decision in April 2007 to fund a 9 week concurrent treatment regimen of Herceptin (trastuzumab) for HER 2 positive early breast cancer patients, and not to fund a 12 month treatment regimen¹.

Of 28 grounds of appeal considered by the Court, 27 were not upheld. However, the Court did find that that PHARMAC ought to have consulted on its July 2006 decision not to fund Herceptin at that time, and for this reason set the July 2006 decision aside.

Given the extensive previous consideration of the matter, the Court has ordered PHARMAC to consult with speed on a new proposal regarding Roche's application for funding 12 months Herceptin for HER 2 positive early breast cancer patients.

The Court found that PHARMAC's decision to fund the 9 weeks concurrent treatment was made appropriately. The decision for funding 9 weeks concurrent treatment with Herceptin therefore remains in place for New Zealand women to access.

We are now consulting on a proposal to decline the funding of 12 months treatment with Herceptin for HER 2 positive early breast cancer. This would mean that Roche's application for funding of 12 months sequential treatment with Herceptin, and proposals relating to the funding of 12 months concurrent treatment with Herceptin, would be declined.

¹ The High Court Judgment can be found at <http://www.pharmac.govt.nz/2008/04/02/090408.pdf>

The available clinical trials for 9 weeks treatment with Herceptin and 12 months treatment with Herceptin have reported similar benefits in terms of cancer-free survival (although it appears that concurrent regimens may be somewhat more efficacious than sequential). We are aware however, that only studies of the 12-month treatment regimens have confirmed that overall survival benefits result from the improvement in cancer-free survival observed in earlier follow up.

The currently funded 9 weeks concurrent treatment regimen costs an estimated \$6 million per year. Funding a 12 month treatment regimen (whether concurrent or sequential) of Herceptin would, at the current price, cost an estimated \$25 million per year, including costs of infusions and other hospital services.

If this proposal to decline the funding of 12 months treatment (whether sequential or concurrent) with Herceptin for HER 2 positive early breast cancer is approved by the Board, PHARMAC would remain open to considering future applications for funding Herceptin for HER 2 positive early breast cancer. This is particularly the case if new information sufficiently demonstrates that an alternate regimen produces additional health gains compared with the currently funded 9 weeks concurrent treatment regimen.

There is uncertainty about the best way to administer (dosing schedule and duration of treatment) Herceptin in HER 2 positive early stage breast cancer, and in our view the optimal regimen cannot be determined from the current evidence.

PHARMAC has been contributing some financial support to a clinical trial since mid-2007 (known as SOLD) for the purpose of obtaining relevant information to help address this uncertainty, and to inform any future decisions regarding Herceptin.

APPENDIX 2: LIST OF SUBMITTERS

- **258** responses from the **general public** generated by completing an online form posted on the **Breast Cancer Aotearoa Coalition (BCAC)** website. Respondents had the option of having their submissions populated with the following pre-prepared statements:
 - “I agree with the Breast Cancer Aotearoa Coalition (BCAC) position that Herceptin should be funded for 12 months for early stage HER2 positive breast cancer; and/or
 - I do not support PHARMAC’s proposal to decline 12 months funding of Herceptin treatment for early stage HER2 positive breast cancer.”

A number of these respondents (approximately 60%) also provided additional personal comments in a free text field; many of these comments contained moving personal accounts of experiences with breast cancer, either as patients, or friends or relatives of breast cancer sufferers. Respondents also had the option to copy a number of third parties in their response, including the Minister of Health.

- **33** other responses from the **general public**, many of which were from breast cancer patients or friends or relatives of breast cancer patients.
- **4** responses from **DHBs** - Lakes, Whanganui, Auckland Regional Oncology Group (representing 3 DHBs) and a collective response from 17 DHBs through DHBNZ.
- **3** responses from **oncologists or oncology organisations** (Dr George Laking, St Marks Private Oncology Clinic, and a collective response from the ANZCS-BSIG),
- **21** responses from other **key stakeholder groups and individuals** including:
 - BCAC
 - Breast Cancer Network NZ
 - NZ Breast Cancer Foundation
 - some of the Judicial Review plaintiffs, the Herceptin Fighting Fund
 - UK Specialised Commissioning Public Health Network (UKCPHN)
 - Roche Products NZ Limited
 - Auckland Women’s Health Council (AWHC)
 - Women’s Health Action Trust (WHAT)
 - The Federation of Women’s Health Councils (FWHC)
 - National Council of Women of New Zealand (NCWNZ)
 - NZ Nurses Organisation (NZNO)

APPENDIX 3: GLOSSARY OF TERMS AND ABBREVIATIONS

TERM	EXPLANATION
Adjuvant	Adjuvant therapy for cancer is surgery followed by chemotherapy and/or radiation treatment
B31	A study of concurrent 12 months Herceptin in HER 2 positive early breast cancer
BCIRG006	A study of concurrent 12 months Herceptin in HER 2 positive early breast cancer
CaTSoP	Cancer Treatments Subcommittee of PTAC.
Concurrent	Herceptin given at the same time as other chemotherapy for the treatment of HER 2 positive early breast cancer
CUA	Cost Utility Analysis
DHB	District Health Board.
FinHER	The Finland Herceptin Study – concurrent 9 weeks Herceptin in HER 2 positive early breast cancer
HERA	The Herceptin Adjuvant Study – sequential 12 months Herceptin in HER 2 positive early breast cancer
MAAC	MedSafes Medicines Assessment Advisory Committee
N9831	A study of concurrent and sequential 12 months Herceptin in HER 2 positive early breast cancer
PACS04	A study of sequential 12 months Herceptin in HER 2 positive early breast cancer
Pharmaceutical	A medicine, therapeutic medical device or related product listed in Sections B to E of the Pharmaceutical Schedule.
Pharmaceutical Schedule	The publication (updated monthly) which lists all the pharmaceuticals which PHARMAC subsidises (fully or partially) with the community pharmaceutical budget.
PTAC	Pharmacology & Therapeutics Advisory Committee.
QALY	Quality Adjusted Life Year – a standard of measurement used when analysing the costs and benefits of a pharmaceutical.
RCT	Randomised Controlled Trials.
Sequential	Herceptin given after completion of other chemotherapy for the treatment of HER 2 positive early breast cancer
Supplier	A company who distributes pharmaceutical products to pharmacies. The supplier should not be confused with the manufacturer of a pharmaceutical; these are often two different companies.

APPENDIX 4: SUMMARY OF AVAILABLE CLINICAL EVIDENCE

The following is a brief summary of the available evidence for Herceptin in HER 2 positive early breast cancer, a more extensive summary of the evidence can be found on our website www.pharmac.govt.nz.

It is not yet clear which way of using Herceptin produces the best results in HER2-positive early breast cancer. Different clinical trials have looked at different ways of using the drug. There are two central questions about how best to use Herceptin:

- Sequencing (before, concurrent with, or after other chemotherapy); and
- Duration (9 weeks, 6, 9, 12 or 24 months treatment).

It is clear that Herceptin provides some additional benefit and risks for some patients over standard chemotherapy alone. Data is continuing to emerge about the magnitude of these benefits and risks and how long they last.

No head-to-head trials have shown whether long or short duration therapy is more effective. However, there are ways to compare the current evidence from the available different trials.

The majority of studies show that Herceptin improves disease-free survival (DFS) compared to standard chemotherapy. In general longer term follow-up data on these studies suggest this benefit may lessen over time.

The main body of evidence for Herceptin in HER2 positive early breast cancer comprises four studies examining concurrent treatment (NCCTG N9831, NSABP B-31, BCIRG006 and FinHer) and three studies examining sequential treatment (HERA, NCCTG N9831 and PACS04). Here is a summary of the results of these main trials:

- HERA trial (sequential 12 months treatment) – when measured after 2 years, compared with standard chemotherapy, for every 100 women treated with Herceptin, six more would avoid having their tumours recur or death (disease events), and nearly two extra deaths from any cause would be avoided.
- NCCTG N9831 Arm B (sequential 12 month treatment) – no benefit (a 1.5% improvement in disease-free survival, which was not significantly better than standard chemotherapy) after 18 months.
- PACS04 (sequential 12 month treatment) – no benefit (a 3.4% improvement in disease-free survival, which was not significantly better than standard chemotherapy; a -0.4% benefit for overall survival, statistically worse than standard chemotherapy) after 4 years.
- Romond/Perez studies, combined data from NSABP B-31 and NCCTG N9831 Arm C (concurrent 12 months treatment) – for every 100 women treated with Herceptin compared with standard chemotherapy, nearly 9 would avoid having their tumours recur or death (disease events), and nearly 3 additional deaths from any cause would be avoided (measured at 3 years follow up).

- BCIRG006 (concurrent 12 months treatment) – for every 100 women treated with Herceptin compared with standard chemotherapy, 6 would avoid having their tumours recur or death (disease events), and nearly 3 additional deaths from any cause would be avoided (measured at 3 years follow up).
- FinHer (concurrent 9 weeks treatment) – for every 100 women treated with Herceptin, compared with standard chemotherapy, nearly 13 more women would avoid having their tumours recur or death (disease events), when measured after three years.

The larger 12 month studies provide greater certainty of the *numerical* accuracy of the evidence, providing greater confidence in the result. Smaller studies, such as FinHer, have wider confidence intervals than larger studies, however the results are still statistically significant and valid and show a good benefit for the funded concurrent 9 week treatment compared with chemotherapy alone.