Technology Assessment Report No. 75,

with supplementary analysis 75b

Trastuzumab (Herceptin) in HER-2 positive early stage primary breast cancer

Part 1: *12-month sequential trastuzumab treatment ("Trastuzumab (Herceptin) in HER-2 positive early breast cancer "),*

August 2006

Part 2: *9 week concurrent trastuzumab treatment in HER-2 positive early breast cancer,*

April 2007

PART 1

Technology Assessment Report No. 75

Trastuzumab (Herceptin) in HER-2 positive early breast cancer

Type: Indicative Cost-Utility Analysis
Last Updated: April 2007 (supplementary analysis 75b); original TAR 75 last updated August 2006.

Summary

This indicative cost-utility analysis examined the cost-effectiveness of adjuvant treatment with trastuzumab (Herceptin) compared with standard treatment for early HER2-positive breast cancer.

Key inputs in the model included reductions in disease breast cancer disease events derived from the published one-year results of the HERA trial; 4-year persistence of effect; an 8% discount rate; quality of life scores based on the HERA trial; and savings due to delays in hospital and other costs with treating fewer recurrences of breast cancer, balanced against the costs of extra cardiac monitoring side effects from trastuzumab. The model was developed with clinical advice from PTAC and expert economic review.

Under the analysis' base case scenario (the assumption of circumstances such as dosage, price, length of benefit etc. considered to be most likely), the cost per QALY was estimated to be between $70,000 and $80,000 (12.5 to 14.3 QALYs gained per $1 million invested). The results of the CUA were very sensitive to the cost of trastuzumab, duration of treatment, the assumed length of benefit (i.e. reduction in risk for recurring breast cancer), and the discount rate used. This resulted in a very wide range of potential values for cost-effectiveness, depending on assumptions and costs incorporated in the analysis.

There is clinical uncertainty with both duration of effect and optimal duration of treatment, and still a number of questions that need to be addressed regarding the use of trastuzumab use in early HER2-positive breast cancer. Hence, based on the available information it is not possible to determine with sufficient certainty whether or not trastuzumab is a cost-effective investment (relative to other pharmaceutical investment options) at this time. In order for trastuzumab to be considered as a cost effective investment, either:

- the overall cost would have to reduce significantly through a reduction in treatment duration (with the same clinical benefit) or through a significant price reduction; or
- the clinical benefit continues to increase following discontinuation of treatment (i.e. the disease free survival curves continue to diverge). It will however be several years before this information is clearly available.

Context

Proposal under assessment

PHARMAC received an application from Roche Pharmaceuticals in December 2005 requesting funding for a 12 month course of trastuzumab (Herceptin) for women with HER2 positive breast cancer following surgery and completion of adjuvant chemotherapy. At the time of the application Medsafe had yet to consider whether to approve this indication for the use of trastuzumab in New Zealand. PTAC considered the application at its 15-16 February 2006 meeting, deciding to defer any recommendation until Medsafe had decided approval for use in early disease. Medsafe granted provisional approval of trastuzumab on 23 March 2006 for the treatment of early HER2 positive breast cancer following surgery and adjuvant chemotherapy.

The current report contains the result of the indicative cost-utility analysis conducted by the Analysis and Assessment team at PHARMAC. The results of this analysis may be considered as part of the decision criteria ('criterion 5') when considering the funding application – where cost-effectiveness is but one of PHARMAC's nine decision criteria.

Description of disease

The application for funding is for one year's treatment with trastuzumab for women with early stage breast cancer, who have tested positive for HER2 over-expression.

Early Breast Cancer
Early breast cancer is described as stage I or II, denoting a tumour of less than 5cm, which may or may not involve moveable same-side axillary lymph node(s), but with no distant metastasis; or a tumour greater than 5cm, if regional lymph nodes are not involved, with no distant metastasis.

The patient population includes:

- women presenting with disease at any age (both pre- and post-menopausal patients);
- those with node-positive as well as node-negative cancer;
- all hormone receptor states (i.e. covers both oestrogen and progesterone positive and negative).

It is however limited to patients who have tested HER2 positive.

There are several different treatment strategies to be aware of for this group of patients (see section 'standard treatment', below).

The standard staging system is that of the American Joint Committee on Breast Cancer (2002) [22]. The system is based on tumour size (T), lymph node involvement (N), and metastatic disease (M).

Table 1: Breast Cancer Stages

Stage	Description
0	TisN0M0
I	T1N0M0
IIa	T0N1M0, T1N1M0, T2N0M0
IIb	T2N1M0, T3N0M0
IIIa	T0-2 N2 M0, T3 N1-2 M0
IIIb	T4 Any N M0
IIIc	Any T N3 M0
IV	Any T Any N M1

Several factors have been shown to be associated with individual patient prognosis, including tumour grade, pathological stage, hormone receptor status and the presence of human epithelial growth factor receptor 2 protein (HER2) over-expression.

HER-2 Positive Disease

Amplification of the HER2/neu oncogene on chromosome 17 causes an increase of HER2 receptor expression on the surface of tumour cells, and results in a constitutively activated growth receptor. These genetic changes occur during the in situ stage of tumour development, and the resulting HER2over-expression phenotype is thought to be fixed for the duration of disease [5].

HER2 positive disease has a documented prevalence of 15-30% [6,7] in breast cancer patients, and has a high prevalence in women aged under 50.

A patient can be identified as positive for HER2 over-expression with laboratory tests (specifically, immunohistochemistry (IHC) and flurescence in-situ hybridisation (FISH)). Evidence has shown that HER2 over-expression is associated with poorly differentiated, high-grade tumours, high rates of cell proliferation and lymph-node involvement, and relative resistance to some kinds of chemotherapy (see 5, for a review). Correspondingly, a positive test result for HER2 over-expression is associated with a poor prognosis. Specifically, HER2 over-expression is associated with approximately 8.5% higher 6 year relapse rate in node negative disease (20.1% rate of relapse compared with 11.6% in those not over-expressing HER2) [9].

PHARMAC analysis of NZ Cancer Register data shows that the above features seem to occur in New Zealand, although missing data make for uncertainty (e.g. 64% of registrations since August 2001 do not have HER2 status recorded)[1] [35]. That said, the available data indicate that 23% of breast cancer registrations in New Zealand with recorded HER2 status are HER2 positive.[2] HER2 positive breast cancer in New Zealand present later than those without HER positivity, consistent with its more aggressive nature and course patterns elsewhere – e.g. 60% of women presenting with HER2-positive breast cancer have disease that is invasive and beyond (Stages C-E), compared with 47% of presentations of breast cancers with HER2 status recorded as negative [35] .

Table 2: Breast cancer registrations August 2001 to December 2005, by HER2 status by stage

Cancer Register breast cancer registrations August 2001 to December 2005

extent of disease		no. registrations HER2 status				percentages	
stage	stage description	HER2 +ve	HER2 -ve	unknown	total	% HER2+ve / known HER2 status	% unknown HER2 status
A	in situ	0	0	1	1		
B	localised	308	1388	3159	4855	18%	65%
C	adj invasion	12	46	98	156	21%	63%
D	regional lymph nodes	418	1108	1917	3443	27%	56%
E	distant	31	76	280	387	29%	72%
F	not known	87	230	1200	1517	27%	79%
total		856	2848	6655	10359		
proportions of overall						23%	64%
% non-localised (C-E)/known stage		60%	47%	42%	45%		
% metastasised (E)/known stage		4.0%	2.9%	5.1%	4.4%		
% unknown stage		10%	8%	18%	15%		

[1] The epidemiology in NZ is complicated by a lack of data. HER2 status has only been recorded in the Cancer Register since August 2001, until recently fewer than 50% of registrations recorded HER2 status – i.e. only now do half of all new cases registered have their HER2 status recorded. Similarly for disease stage information – there are substantial gaps with non-recording of stage at time of registration (once on the register, stage is not updated; the only longitudinal outcome data recorded is date of death).

[2] Note however that as the rate of recording HER2 status in the NZ Cancer Register has gradually increased with time, the proportions of HER2-positive breast cancers of known status has declined.

Pharmaceutical under Assessment

Trastuzumab (Herceptin) is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the extra-cellular domain of HER2 protein. Although the exact mechanism of action remains unclear, it is thought that antibody binding is associated with a variety of both extracellular effects (for example, immune mechanisms), and changes in intracellular signalling (for example, induction of apoptosis, decreased cell proliferation), which confer the clinical benefits (i.e. reduction in tumour size and a reduced risk of relapse) (see 5, for a review).

Trastuzumab is administered as a 90-minute intravenous (IV) infusion, at a loading dose of 8 mg/kg, then 6 mg/kg every three weeks for 52 weeks. Patients need to be observed for symptoms (e.g. fever) for at least six hours after the start of the first infusion, and for two hours after the start of subsequent infusions [10].

Trastuzumab is currently approved and funded under Special Authority for use in New Zealand for patients with metastatic breast cancer. The current Special Authority criteria for trastuzumab are as follows [11]:

Product	Special Authority Criteria
Trastuzumab	Special Authority for Subsidy – Form SA0778 Initial application only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria: 1. The patient has metastatic breast cancer expressing HER-2 3+ or FISH+ Renewal only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria: 1. The cancer has not progressed.

On 23 March 2006 Medsafe announced provisional approval for trastuzumab for the treatment of women with early breast cancer who test positive for the HER2 gene once they have had surgery and completed adjuvant chemotherapy. The provisional approval limited treatment to those women who have a normal heart function before treatment starts and requires women using trastuzumab to have their heart function checked by echocardiogram every three months during treatment.

Standard treatment

Current therapy for early breast cancer in New Zealand initially involves loco-regional therapy (surgery and/or radiotherapy), followed by between four and eight cycles of adjuvant chemotherapy (usually an anthracycline based regimen), hormone therapy (in patients with hormone receptor positive disease), or a combination of these treatments.

Hormonal treatments are used in patients with hormone receptor-positive tumours (about 60% of patients), both in early stage disease (as adjuvant therapy) and in advanced disease (as palliative therapy). Adjuvant hormonal therapy (e.g. tamoxifen) is usually administered for 5 years. If hormone receptor-positive patients cannot tolerate or are contraindicated to tamoxifen, they receive an aromatase inhibitor (letrozole or anastrozole).

Prior to the introduction of trastuzumab, the treatment protocols for HER2 positive patients followed those of HER-2 negative disease (i.e. there has not been an individual therapy protocol for patients with HER2 over-expression).

Clinical Inputs

Data sources

Search strategy

TRIP (http://www.tripdatabase.com/) and PubMed searches for randomised controlled trials, review articles, meta-analyses, guidelines and economic analyses of [trastuzumab] or [Herceptin] for early breast cancer. Key words included [clinical effectiveness], [relapse] and [cost effectiveness]. The search was supplemented by material supplied by Roche in its application to PHARMAC for the funding of trastuzumab for early breast cancer.

Source data used in this analysis

The key systematic review cataloguing RCT evidence was the NHSC report [28], which in turn catalogued the RCT evidence at the time [1, 2, 3, 4]. There was also the material supplied by Roche in its application to PHARMAC for the funding of trastuzumab for early breast cancer, and one published economic evaluation [30] identified.

We searched for quality of life data for breast cancer in the above sites, using the key words "breast cancer", "quality", "quality of life", "economic analysis", "cost-effectiveness", "cost-utility", "QALY*" and "quality-adjusted life years". We supplemented this with examination of sources of community-derived generic quality of life scores [24, 25, 26, 27].

Detailed assessment of key clinical trials was made separately by the Pharmaceutical and Therapeutics Committee (PTAC) as part of its considerations of trastuzumab in February 2006 and later in May 2006. PTAC's assessments informed the clinical inputs into the PHARMAC model.

Outcome measures

Effectiveness

Breast cancer disease-free survival, total survival, recurrence rates.

Withdrawals, discontinuations and adverse effects

Cardiac toxicity (including symptomatic heart failure, decreased LVEF), serious infection, other serious adverse events.

Criteria for including or excluding source data

Effectiveness

Randomised controlled trials of trastuzumab in the treatment of early breast cancer; excludes metastatic disease.

Quality of life

Breast cancer QoL studies using generic health related quality of life scores.

Expert input

As well as PTAC's considerations informing the PHARMAC model, the structure, assumptions and results of the initial modelling were reviewed by an international expert.

Levels of evidence

PHARMAC uses a modification of the Revised Scottish Intercollegiate Guidelines Network (SIGN) grading system [29]:

1++	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies; High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3a	Non-analytic uncontrolled observational studies
3b	Case reports
4	Expert opinion and/or modelling in absence of empirical data

The above levels derive from four overall levels of evidence, and with overall levels 1 and 2 each subdivided into three quality-rated sublevels:

Level 1	Randomised controlled clinical trials
Level 2	Non-randomised controlled analytical studies (non-randomised interventional, observational cohort, case-control)
Level 3	Non-analytic uncontrolled observational studies (cross sectional studies, prospective longitudinal follow-up studies, retrospective follow-up case series, case reports)
Level 4	Expert opinion and/or modelling in absence of empirical data
++	All or most criteria are met; Where criteria are not met, conclusions are thought very unlikely to alter.
+	Some of criteria are met; Where criteria are not fulfilled or are not adequately described, conclusions are thought unlikely to alter.
– (minus)	Few or no criteria are met; Where criteria are not fulfilled or are not adequately described, conclusions are thought likely or very likely to alter.

Supporting documents

Appendix One: PTAC minutes February 2006
Appendix Two: PTAC minutes May 2006

Efficacy

At the time the model was developed, PHARMAC and PTAC were aware of four key randomised controlled trials published on the efficacy of trastuzumab in HER2-positive early breast cancer.

Interim results (one year follow-up) of the Herceptin Adjuvant (HERA) Trial study were published in the New England Journal of Medicine in October 2005 [1]. This open-label randomised controlled trial (RCT) evaluated the efficacy of trastuzumab after completion of chemotherapy in 1694 women with early breast cancer.

The results of two further trials on trastuzumab in early breast cancer were combined and published in October 2005 [2]. These trials evaluated the efficacy of trastuzumab when administered at the same time as chemotherapy.

Subsequent to the completion of the draft analysis, results of a trial were published in February 2006 using a 9-week adjuvant course of trastuzumab [36]. This trial (FinHer) is described in the Discussion section of this report.

As the application from Roche is for funding trastuzumab after completion of adjuvant chemotherapy using a one-year course, this assessment is based on the interim results of the HERA trial.

Trastuzumab AFTER adjuvant chemotherapy (12 months treatment)

There has been one large (n=3387) open-label randomised controlled trial on trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer [1]. Details of the HERA trial are outlined in the table below:

Table 3: HERA Trial Details

	HERA [1]
Study Design	Open-label RCT
Level of Evidence	1- (Meta analyses, systematic reviews, or RCTs with a high risk of bias)
Disease category	HER2 positive early breast cancer
Patient group	Women with early breast cancer who had completed locoregional therapy and chemotherapy, and tested HER2 positive.
Intervention	1 year trastuzumab therapy (every three weeks) n=1,694 Loading dose: 8mg/kg; maintenance doses: 6 mg/kg
Comparator	Observation (placebo) n=1,693
Follow-up	1 year median follow-up
Primary Endpoint	Disease-free survival (DFS)
Modified Jadad score [23]	3/5. Randomisation, concealment of allocation and follow-up appear to be adequate. However, there is no information on the blinding of receipt, blinding of provision or blinding of assessment.
Results	Summarised in the table 4

The interim (1-year) results of the HERA trial were based on 3387 patients. There were 127 (7.5%) primary endpoint events in patients administered trastuzumab compared with 220 (13.0%) in the observation arm (absolute reduction of 5.5%, number needed to treat 18). Estimated 2-year disease-free survival was 85.5% and 77.4% in the trastuzumab and observation arms, respectively.

The trial reported no significant difference in overall survival. Estimated 2-year survival was 96.0% and 95.1% in the trastuzumab and observation groups, respectively.

Subgroup analysis indicates that the effect of trastuzumab is independent of age, nodal involvement, hormone receptor status, or type of adjuvant chemotherapy.

Table 4: Event Rates from HERA Trial

Events	Trastuzumab	Observation
Primary events	127 (7.5%)	220 (13.0%)
Estimated 2-year DFS	85.5%	77.4%
Mortality	29 (1.7%)	37 (2.2%)
Estimated 2-year overall survival (OS)	96.0%	95.1%

The Pharmacology and Therapeutic Advisory Committee (PTAC) noted at its February 2006 meeting that this is an interim analysis (1 year follow-up of a planned 2-year study), and also that this was an unblinded study. Further details of PTAC's considerations can be found in Appendices One and Two.

Trastuzumab PLUS adjuvant chemotherapy

The combined interim analysis of the North Central Cancer Treatment Group (NCCTG) Protocol N9831 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B31, were published in October 2005 [2].

In both studies women were treated with doxorubicin, cyclophosphamide and paclitaxel (or a similar regimen with trastuzumab). The study does not state whether patients were blinded.

Table 5: NCCTG and NSABP Trial Details

	North Central Cancer Treatment Group (NCCTG) Protocol N9831 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B31 [2]
Study Design	Open-label RCTs
Levels of Evidence	1- (Meta analyses, systematic reviews, or RCTs with a high risk of bias)
Disease category	HER2 positive early breast cancer
Patient group	Women with early breast cancer who had completed locoregional therapy and tested HER2 positive.
Intervention	Trastuzumab (1 year) and concurrent chemotherapy B31 n=864 (patients with follow-up) N9831 n=808 (patients with follow-up) Protocol: loading dose 4mg/kg; weekly doses of 2 mg/kg for 51 weeks
Comparator	Observation (placebo)
Follow-up	2 years median follow-up (2.4 years for B31 and 1.5 years for N9831)
Primary Endpoint	Disease free survival (DFS)
Modified Jadad scores [23]	3/5, 3/5. Randomisation, concealment of allocation and follow-up appeared to be adequate in both trials. However, neither reported on the blinding of receipt, blinding of provision or blinding of assessment.
Results	Summarised in the table below

After a median follow-up of 2 years (2.4 years in NSABP-B31 and 1.5 years in NCCTG-N9831) there were 133 (8.0%) primary events in the trastuzumab groups, compared with 261 (15.5%) events in the CT only groups (absolute reduction of 7.5%, NNT 13 over 2 years).

The improvement in overall survival in patients administered trastuzumab compared with CT only was statistically significant at two years.

Table 6: Event Rates from NCCTG and NSABP Trials

Events	Trastuzumab	CT only
Primary events	133 (8.0%)	261 (15.5%)
Distant metastases	96 (5.7%)	193 (11.5%)
Estimated 3-year DFS	87.1%	75.4%
Estimated 4-year DFS	85.3%	67.1%
Deaths	62 (3.7%)	92 (5.5%)
Estimated 3-year OS	94.3%	91.7%
Estimated 4-year OS	91.4%	86.6%

At its February 2005 meeting, PTAC noted that the results of each of these trials had not been published separately. They considered that, rather than a pooled analysis being published, each trial should have been published individually, with a subsequent meta-analysis (rather than a pooled analysis). Members noted that there were some significant differences between the papers that make comparisons difficult, such as the timing of paclitaxel and disparate use of hormonal and radiation therapies. Members also noted that both of these trials were unblinded.

PTAC also noted that the results of Group B of study N9831 were not included in the report, and that this was the only arm in the two studies that was of direct relevance to the current application. Members considered that the efficacy results of this paper were therefore of limited value. In addition, the Committee considered that while it was plausible that that disease-free survival could translate into overall survival in the long-term, there is insufficient evidence upon which to extrapolate this benefit reliably.

Further details of PTAC's considerations can be found in Appendices One and Two.

Trastuzumab AFTER/PLUS adjuvant chemotherapy

The Breast Cancer International Research Group (BCIRG) 006 assessed the efficacy of three treatment regimes – chemotherapy followed by trastuzumab plus docetaxel, chemotherapy plus trastuzumab, chemotherapy followed by docetaxel alone. The full results have not yet been published in a peer-reviewed medical journal, however interim analysis has been reported at conferences and in media reports [3,4].

Table 7: BCIRG 006 Trial Details

	Breast Cancer International Research Group (BCIRG) 006 [3,4]
Study Design	Phase III trial
Disease category	HER2 positive early breast cancer
Patient group	HER2 positive women with early breast cancer who had completed locoregional therapy and chemotherapy (n=3,222)
Intervention	Doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC arm) Docetaxel and carboplatin chemotherapies plus trastuzumab (TCH arm)
Comparator	Doxorubicin and cyclophosphamide followed by docetaxel alone.
Follow-up	Not stated
Primary Endpoint	Reduction in risk of disease recurrence
Modified Jadad score [23]	Not assessable (preliminary data in form of press release)
Results	Interim results that were available summarised in the Table 8

Event rates from the BCIRG trial are reported in the table below.

Table 8: Event Rates from BCIRG Trial

Events	AC/ trastuzumab/ docetaxel	Docetaxel/ carboplatin/ trastuzumab/	AC/ docetaxel
Reduction in risk of disease recurrence (compared with AC/docetaxel)	51% (35%-65%)	39% (21%-53%)	---
Significant cardiac events	2.3%	1.2%	1.2%

Trastuzumab in association with adjuvant chemotherapy (9 weeks treatment administered before FEC)

The FinHer trial [36] assessed the effects of a 9-week adjuvant course of trastuzumab. This trial is described in the Discussion section of this report.

Summary of Clinical Evidence

Evidence to date indicates that trastuzumab results in a reduction in the risk of disease relapse. It is not yet known if this translates into improved overall survival (OS). The combined B-31/N9831 reported a statistically significant improvement in OS in patients administered trastuzumab. However, the difference in OS in the HERA trial was not statistically significant.

It needs to be highlighted that the published data are interim and hence should be interpreted with caution.

Safety

The key safety concern associated with trastuzumab is the small but significant increased risk of developing cardiotoxicity. This risk appears to be higher when trastuzumab is administered with concurrent anthracycline-based CT than when it is administered after chemotherapy is complete.

The 1-year interim results of the HERA study report that 7.9% of patients in the trastuzumab arm, and 4.4% of patients in the observation arm had at least one grade 3 or 4 adverse event, including infection (1.3% vs 0.4% in trastuzumab and observation group, respectively), severe congestive heart failure (CHF) (0.54% vs 0%, p=0.002, in trastuzumab and observation group, respectively), symptomatic CHF (1.73% vs 0.06%, p<0.001, in trastuzumab and observation group, respectively). There were no deaths, attributed to cardiotoxicity, however longer-term follow-up is necessary to quantify the risk of cardiotoxicity [1].

The three other trails also reported an increased risk of cardiotoxicity in trastuzumab treated patients. In the B-31/N9831 trials, 31.4% of patients discontinued treatment prior to 1 year, with 14.2% reported as discontinuing due to confirmed asymptomatic decline in left ventricular ejection fraction (LVEF), 4.7% due to symptoms of CHF or other adverse cardiac effect, and 6.0% patient-initiated discontinuation.

Overall, it appears that trastuzumab is less cardiotoxic with sequential treatment than concurrent treatment, however longer-term data is needed to confirm this.

It is important to note that even though the incidence of symptomatic CHF and cardiac death were low in these trials, these figures were obtained through careful patient selection, intensive cardiac assessment and drug withdrawal [5]. It is not known how high the risk of cardiotoxicity would be when administered in clinical practice.

The mean half-life of trastuzumab is 28.5 days (95% CI, 25.5-32.8 days), and it may remain in the circulation for up to 20 weeks (95% CI, 18-24 weeks) after stopping

treatment (Roche Datasheet). Therefore there is a concern that toxicity may be ongoing after ceasing therapy.

It is not certain if trastuzumab-induced cardiotoxicity is reversible, and if so, the time course of any reversibility [5]. There are some studies in the literature that examine the nature of trastuzumab related cardiotoxicity. The details of these are summarised in the table below.

Table 9: Studies on Trastuzumab-Related Cardiotoxicity

Authors	Outcome
Ewer et al., 2005 **J Clin Oncol 2005 23(31):7820-26 [12]**	38 patients with HER2 +ve breast cancer and suspected trastuzumab related cardiotoxicity. Mean time to recovery of LVEF was 1.5 months. LVEF increased in 37 out of 38 patients. 88% (22) patients required medical treatment. 9 patients underwent endomyocardial biopsy and ultrastructural changes were not seen. 25 patients (66%) who were rechallenged continued their heart failure drug regimens when trastuzumab was introduced (maximum tolerated doses of angiotensin-converting enzyme inhibitors and beta-blockers). The median duration of reintroduced trastuzumab therapy was 8.4 months. LV dysfunction and/or CHF occurred in three of these patients (12%), and trastuzumab treatment was permanently discontinued in these patients.
Vogel et al., 2002 **J Clin Oncol 2002 (3):719-726 [13]**	This study was a randomised, single-blind, multicentre study to evaluate the efficacy and safety of 2 dose levels of trastuzumab as a first line therapy in women who did not wish to receive cytotoxic chemotherapy for metastatic breast cancer (note: many (68%) had previously received a form of chemotherapy). Doses: LD 4mg/kg, then 2mg/kg weekly (n=59), or LD 8mg/kg, then 4mg/kg weekly (n=55). Median number of doses: 16 All cardiac events were reviewed retrospectively by an independent, blinded committee. Cardiac dysfunction occurred in 2 patients (2%). Both had a history of cardiac disease and did not require additional intervention after discontinuation of trastuzumab. Adverse events occurred in all but one patient. The most common treatment related adverse effects were: chills (25%), asthenia (23%), fever (22%), pain (18%), and nausea (14%).

The small sample sizes and disparate natures of these trials mean that the full economic impact and patient risk associated with trastuzumab cardiotoxicity in clinical practice cannot be measured conclusively.

An increased frequency of brain metastases has also been reported among patients with metastatic breast cancer treated with trastuzumab. In the B-31 and N9831 trials the incidence of brain metastases as a first event was higher in the trastuzumab group than the control group (21 vs. 11 in B-31, and 12 vs. 4 in the N9831 trial). Brain metastases as a first or subsequent event were diagnosed in 28 patients in the trastuzumab group, compared with 35 in the control group (hazard ratio, 0.79; p=0.35). Therefore, the imbalance in the first measure was attributed to earlier failures at other distant sites in the control group [2].

Rare cases of interstitial pneumonitis have been reported in patients that appear to relate to trastuzumab therapy. Four patients in the trastuzumab group of the B-31 trial developed interstitial pneumonitis, one of whom died. Similarly in the N9831 trial, five patients in the trazstumuzab group developed grade 3+ pneumonitis, or pulmonary infiltrates, one of whom died. As this adverse effect was not reported in the HERA trial, it may be only be associated with the therapeutic regimens that combines trasutuzumab and chemotherapy.

Other common (reported in >10% of patients) adverse events that have been associated with the use of trastuzumab include: abdominal pain, asthenia, chest pain, chills, fever,

headache, pain, diarrhoea, nausea, vomiting, arthralgia, myalgia and rash. It is also noted that anaphylactoid reactions have occurred on rare occasions with trastuzumab use [11,12].

International Recommendations / Guidelines

As the key clinical trials on the efficacy of trastuzumab in early breast cancer were published in late 2005, at the time of writing few international clinical guidelines had been published regarding the use of trastuzumab in early breast cancer.

In the United States, The National Comprehensive Cancer Network (NCCN) has recently added HER2 testing and the use of targeted trastuzumab therapy to their guidelines for treatment of early breast cancer [15]. The London Cancer New Drugs Group agreed that firm recommendations on the use of trastuzumab in early breast cancer cannot be made at present on the basis of the current data, due to the complexity of balancing the potential benefits and risks of treatment, especially regarding the serious adverse cardiac effects [17].

The National Institute of Health and Clinical Excellence (NICE) in the United Kingdom issued a draft recommendation to support the use of trastuzumab in early breast cancer in the UK [16]. Pending the results of an appeal, the recommendation is expected to be finalised in August 2006, which means Primary Health Trusts would be obliged to provide funding from October 2006 (however treatment may be provided earlier).

Cost-Utility Analysis

Introduction

Perspective

This analysis was conducted from perspective of the DHB (the funder of hospital pharmaceuticals) and included estimated direct medical costs.

The purpose of this cost-utility analysis is to estimate the incremental cost-utility of trastuzumab compared with standard treatment in patients with early HER2 positive breast cancer.

Target Population

The target population for this analysis is defined as women with early breast cancer who have completed loco-regional therapy (surgery and/or radiotherapy) and at least four cycles of adjuvant chemotherapy, and have tested IHC (3+) or FISH-positive for HER2 overexpression. This group includes both those with hormone-receptor negative, and hormone-receptor positive disease.

Comparator

The comparator for the analysis is standard treatment for women with early breast cancer following surgery and chemotherapy. For hormone-receptor positive patients, treatment usually consists of tamoxifen (or an aromatase inhibitor if tamoxifen is contra-indicated or not tolerated). Hormone-receptor negative patients generally do not receive further treatment after chemotherapy. Approximately 50% of patients in the HERA trial were hormone-receptor positive. It is assumed that 80% of hormone-receptor positive patients would receive tamoxifen, and 20% would receive an aromatase inhibitor.

Level of Analysis

The following analysis is an indicative analysis. Note that PHARMAC undertakes four levels of economic analysis: rapid, preliminary, indicative, and detailed. A description of these levels is included in the table below. In a pragmatic public policy/purchasing environment with finite analytical capacity, there are inevitable trade-offs between precision and timeliness. The level (extent and depth) of economic analysis varies according to individual policy issues, availability of analyst resources at the time, the defensibility of any recommendations derived from the results, and the extent of information available for analysis.

Table 10: Taxonomy of economic analyses undertaken by Pharmac

Type	Description
Detailed	Includes a detailed and systematic identification and synthesis of effectiveness, health-related quality of life, and cost data. Requires on average 3-6 months of full-time analyst input. Reviewed internally (PTAC for clinical assumptions) and externally.
Indicative	An interim assessment using some opportunistic data, but more detailed than a preliminary analysis. These typically require 4-6 weeks of full-time analyst input. Typically reviewed internally and by PTAC.
Preliminary	A rapid assessment largely using opportunistic data. Likely to take 1-2 weeks' analyst input
Rapid	A very rapid assessment using opportunistic data, usually involving 1-2 days' full-time analyst input. Includes supplier analyses that have not yet been evaluated by PHARMAC staff.

This indicative analysis is based on the broad principles used by PHARMAC for pharmacoeconomic evaluations as described by the Recommended Methods to Derive

Clinical Inputs for Proposals to PHARMAC (available at http://www.pharmac.govt.nz/pdf/62465.pdf) and PHARMAC's Prescription for Pharmacoeconomics (available at http://www.pharmac.govt.nz/pharmo_economic.asp). These principles currently include: the use of overall health sector costs and direct patient costs when measuring effects on overall costs; measuring QALY gains; discounting both costs and QALY gains according to PHARMAC's current discount rate [8%]; use of univariate and multivariate sensitivity analyses; and the systematic identification, synthesis and presentation of relevant clinical input data. Note however that this as an indicative analysis and that some data are derived opportunistically, not systematically.

Cost-Utility Analysis

A Markov model was constructed to model the different treatment strategies. This model uses data derived from the HERA trial, as this is the only published trial where patients received trastruzumab following chemotherapy (and is therefore the only relevant evidence for the current proposal).

The costs were in New Zealand dollars. The primary measure of effect was quality-adjusted life years (QALYs) and the principal outcome was the incremental cost per QALY. Costs and benefits are discounted using a discount rate of 8%, as per the methods described in PHARMAC's Prescription for Pharmacoeconomic Analysis (PFPA).

Time Horizon

The time horizon for the model was the life-time of patients with early breast cancer (i.e. the model was run until all patients were in the absorbing state). Each Markov cycle was 6 months (average length of chemotherapy treatment if a patient relapses). Patients receive treatment with trastuzumab for 12 months (or 2 cycles), unless they experience a severe adverse event or relapse within this time period, resulting in discontinuation prior to 12 months.

A half-cycle correction was only applied to patients entering the death stage, where half the cost and benefit of the last cycle was removed. This means that patients are assumed to die in the middle of the cycle, but that all other transitions are occurring at the end of each cycle. Note that as the majority of costs are in the first two cycles, a standard half-cycle adjustment would result in an underestimate of the true cost of trastuzumab.

Model Structure

The Markov model was based on the following structure:

- patients entering the model have early stage breast cancer and have not yet been tested for HER2 status;
- patients are randomised to receive trastuzumab or no trastuzumab treatment (as occurred with the placebo arms of the clinical trials);
- patients randomised to receive trastuzumab will be tested for HER2 over-expression and cardiac risk;
- patients receive trastuzumab if HER2 positive (18 to 25% of patients with early breast cancer), and if they are not at risk of a cardiac event;
- the baseline risk of a cardiac event was based on the age distribution of patients (see below);
- treatment with trastuzumab is for two cycles (12 months), unless patients develop a severe adverse event or relapse, resulting in discontinuation of treatment.

The key outcomes considered in the analysis were:

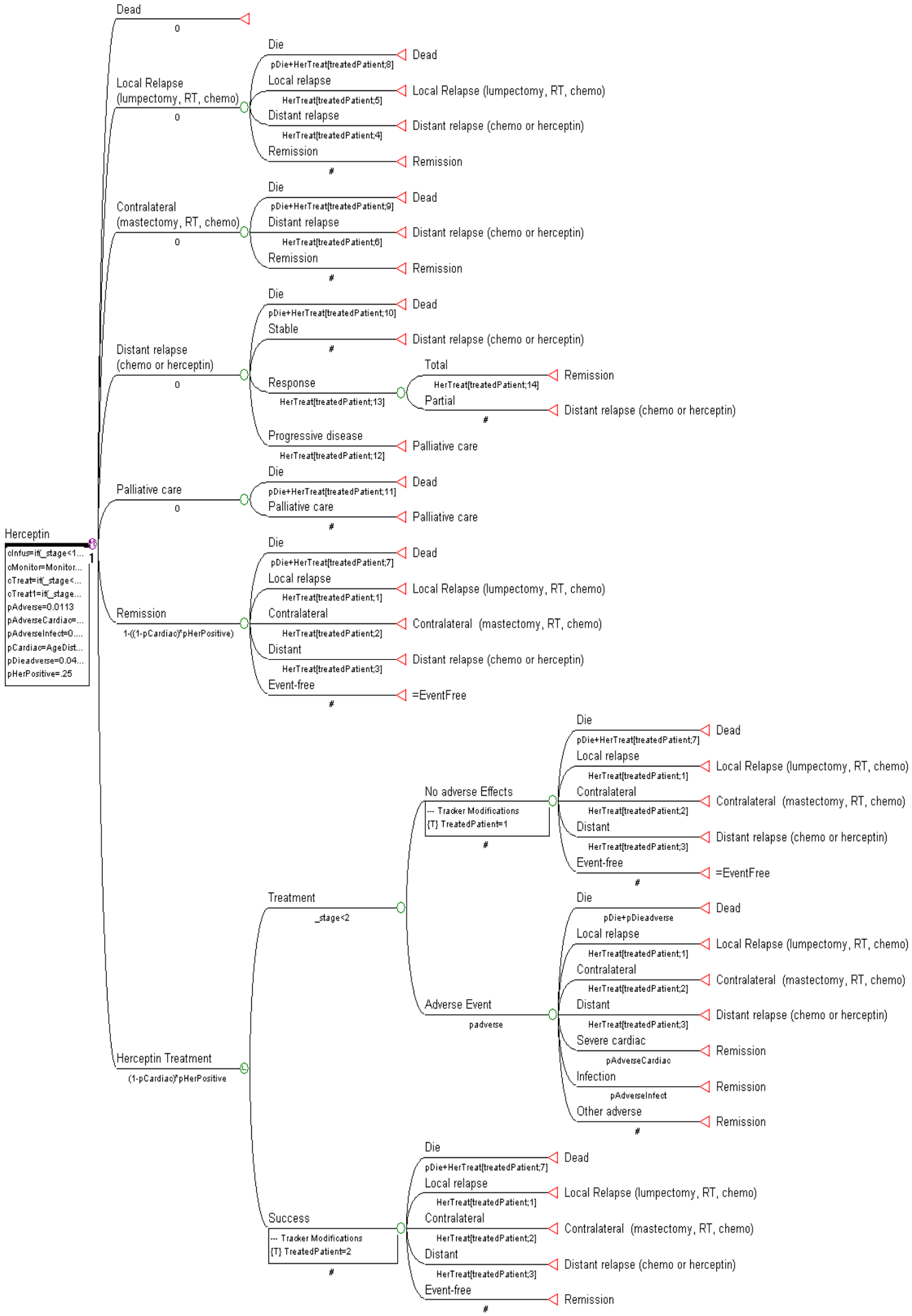
- severe adverse effects – infection, cardiac toxicity (severe heart failure) and other severe adverse events;
- breast cancer relapse – local, contralateral, distant;
- breast cancer remission; and
- death.

The base-case analysis assumes that patients' administered trastuzumab will have continued benefit from treatment (in terms of reduced relapse rates) for four years (i.e. three years after cessation of treatment). While the data from the HERA trial only report a median follow-up of one year after treatment cessation, a small group of patients in the Romond trial have been shown to benefit from trastuzumab when followed for up to four years (three years after completion of trastuzumab treatment) [2].

The analysis also considers the following scenarios:

1. treatment benefits continue after cessation of therapy for the expected lifetime of the patient;
2. treatment benefits last two years, then adopt rates relating to the comparator (i.e. hormonal therapy/no treatment);
3. patients require two years treatment with trastuzumab in order to obtain increased benefit (in terms of reduced rate of relapse) for four years.

A branch of the Markov model is included on the following page (note that this is a simplified version).


Herceptin
cInfus=if(_stage<1...
cMonitor=Monitor...
cTreat=if(_stage<...
cTreat1=if(_stage...
pAdverse=0.0113
pAdverseCardiac=...
pAdverseInfect=0....
pCardiac=AgeDist...
pDieadverse=0.04...
pHerPositive=.25
1
Dead
0
Local Relapse (lumpectomy, RT, chemo)
0
Die
pDie+HerTreat[treatedPatient;8]
Dead
Local relapse
HerTreat[treatedPatient;5]
Local Relapse (lumpectomy, RT, chemo)
Distant relapse
HerTreat[treatedPatient;4]
Distant relapse (chemo or herceptin)
Remission
#
Remission
Contralateral (mastectomy, RT, chemo)
0
Die
pDie+HerTreat[treatedPatient;9]
Dead
Distant relapse
HerTreat[treatedPatient;6]
Distant relapse (chemo or herceptin)
Remission
#
Remission
Distant relapse (chemo or herceptin)
0
Die
pDie+HerTreat[treatedPatient;10]
Dead
Stable
#
Distant relapse (chemo or herceptin)
Response
HerTreat[treatedPatient;13]
Total
HerTreat[treatedPatient;14]
Remission
Partial
#
Distant relapse (chemo or herceptin)
Progressive disease
HerTreat[treatedPatient;12]
Palliative care
Palliative care
0
Die
pDie+HerTreat[treatedPatient;11]
Dead
Palliative care
#
Palliative care
Remission
1-((1-pCardiac)*pHerPositive)
Die
pDie+HerTreat[treatedPatient;7]
Dead
Local relapse
HerTreat[treatedPatient;1]
Local Relapse (lumpectomy, RT, chemo)
Contralateral
HerTreat[treatedPatient;2]
Contralateral (mastectomy, RT, chemo)
Distant
HerTreat[treatedPatient;3]
Distant relapse (chemo or herceptin)
Event-free
#
=EventFree
Herceptin Treatment
(1-pCardiac)*pHerPositive
Treatment
_stage<2
No adverse Effects
--- Tracker Modifications
{T} TreatedPatient=1
#
Die
pDie+HerTreat[treatedPatient;7]
Dead
Local relapse
HerTreat[treatedPatient;1]
Local Relapse (lumpectomy, RT, chemo)
Contralateral
HerTreat[treatedPatient;2]
Contralateral (mastectomy, RT, chemo)
Distant
HerTreat[treatedPatient;3]
Distant relapse (chemo or herceptin)
Event-free
#
=EventFree
Adverse Event
padverse
Die
pDie+pDieadverse
Dead
Local relapse
HerTreat[treatedPatient;1]
Local Relapse (lumpectomy, RT, chemo)
Contralateral
HerTreat[treatedPatient;2]
Contralateral (mastectomy, RT, chemo)
Distant
HerTreat[treatedPatient;3]
Distant relapse (chemo or herceptin)
Severe cardiac
pAdverseCardiac
Remission
Infection
pAdverseInfect
Remission
Other adverse
#
Remission
Success
--- Tracker Modifications
{T} TreatedPatient=2
#
Die
pDie+HerTreat[treatedPatient;7]
Dead
Local relapse
HerTreat[treatedPatient;1]
Local Relapse (lumpectomy, RT, chemo)
Contralateral
HerTreat[treatedPatient;2]
Contralateral (mastectomy, RT, chemo)
Distant
HerTreat[treatedPatient;3]
Distant relapse (chemo or herceptin)
Event-free
#
Remission

Age distribution

The analysis uses the age (year)- and HER2 receptor-specific distribution of those women registered in the New Zealand Cancer Register with breast cancer between August 2001 (when HER2 status was included as a field in the Cancer Register) and 31 December 2005, where there were 10359 women registered with breast cancer (median age 58 years).[3] In clinical practice, women aged 70 years and over may be less likely to choose to receive chemotherapy and therefore trastuzumab. As a proxy for this, for modelling purposes only, the analysis is restricted to those aged up to and including 79 years. Restricting the analysis to patients aged less than 80 years favours trastuzumab, as younger patients dying prematurely of breast cancer lose greater life potential than older patients, hence trastuzumab would confer greater benefits for younger patients.

The analysis also assumes in clinical practice that age-specific proportions of women who develop early breast cancer and also have cardiovascular risk factors will either not be offered treatment, or will themselves decide not to have trastuzumab treatment because of their associated cardiac risk. This is in line with the exclusion criteria of the relevant clinical trials [1,2] and Medsafe's cautions over the potential for trastuzumab to exacerbate heart failure. The analysis proxies these proportions using survey-derived estimates of the age-specific prevalence of pre-existing cardiovascular disease in New Zealand women.[4] Since cardiac risk increases with age, excluding these patients means the age distribution becomes younger. (Restricting the analysis to patients without pre-existing cardiovascular disease favours trastuzumab, as these patients will be younger than may occur in clinical practice. Despite the Medsafe approval criteria, PHARMAC have no evidence to suggest that, in New Zealand clinical practice, patients with cardiovascular risk factors may be offered, and accept trastuzumab treatment. Therefore, this analysis may underestimate the actual incidence and implications of trastuzumab-related cardiac toxicity in this population.

Combining both the 79-year upper age limit and exclusion of any cardiovascular risk gives a population of women with HER2 positive breast cancer with a median age of 50 years (see table below). Note the median age in each of the two key clinical trials [1,2] was 49 years.

[3] PHARMAC analysis of Cancer Register data for female breast cancers 1991 to 2005, supplied by NZHIS

[4] Wells S, Broad J, Jackson R. Estimated prevalence of cardiovascular disease and distribution of cardiovascular risk in New Zealanders: data for healthcare planners, funders, and providers. N Z Med J. 2006 Apr 21;119(1232):U1935. http://www.nzma.org.nz/journal/119-1232/1935/content.pdf Table 1. Prevalence and risk of cardiovascular disease in New Zealand population, by age and sex. Prior CVD estimates based on smoothed rates from Auckland Heart & Health Survey (1992-3 data for non-Maori, non-Pacific people), for age & sex groups, and includes self-reported heart attack (with hospital admission) or stroke, angina (on nitrates), but not PVD, PTCA, CABG or genetic lipid disorder.

Table 11: Age distribution of HER2 Positive Patients with Early Breast Cancer Likely to receive Trastuzumab (from Cancer Registry data August 2001 to December 2005, combined with estimates of CVD prevalence)

since 8/2001

no. registrations	her2_status				pre-existing CVD	
5-yr agegroup	**HER2 +ve**	HER2 -ve	unknown	total	possible %	**no. pts HER2 +ve w/o CVD**
15-19			2	2		**0**
20-24	**3**	2	2	7		**3**
25-29	**11**	13	22	46		**11**
30-34	**48**	72	90	210		**48**
35-39	**62**	121	245	428	0.1%	**62**
40-44	**99**	287	460	846	0.2%	**99**
45-49	**119**	400	696	1215	0.3%	**119**
50-54	**144**	439	882	1465	1.9%	**141**
55-59	**116**	383	800	1299	3.3%	**112**
60-64	**110**	318	844	1272	6.3%	**103**
65-69	**45**	270	635	950	11.3%	**40**
70-74	**39**	203	561	803	17.2%	**32**
75-79	**32**	160	527	719	23.5%	**24**
80-84	13	120	428	561	26.2%	
85-89	13	43	281	337	26.7%	
90-94	1	16	141	158		
95-99	1	1	35	37		
100-104			4	4		
total	856	2848	6655	**10359**		
subtotal, aged <80	**828**	2668	5766	9262		**795**
median age	52.0	56.0	60.0	**58.0**		
median age, aged <80	**51.0**	54.5	58.0	56.0		**50.0**
mean age, aged <80	**52.1**	55.3	57.6	56.5		**49.4**

Severe Adverse Events

The risk of developing a severe adverse event was based on the rates reported in the HERA trial (patients with at least one serious adverse event).

Approximately 117 (7%) of patients receiving trastuzumab, and 81 (4.7%) of those receiving placebo, developed a severe adverse event. The analysis considered the proportion of adverse events that were due to infection and cardiac toxicity, in order to model these as separate health states. This is outlined in the table below:

Table 12: Adverse Events in HERA Trial

	Trastuzumab (N=1677)	**Placebo (N=1710)**
Severe adverse event	177 (7.0%)	81 (4.7%)
- Infection	29 (24.8%)	10 (12.4%)
- Cardiac event	17 (14.5%)	4 (4.9%)
- Other	71 (60.7%)	67 (79.0%)

For patients receiving trastuzumab, 29 (24.8%) of severe adverse events were due to infection, and 14.5% due to cardiac toxicity. In placebo patients, 12.4% of severe adverse events were due to infection, and 4.9% cardiac toxicity). The remaining severe adverse events (60.7% trastuzumab, 79.0% placebo) were grouped into 'other adverse events'. The HERA trial does not provide details on these other severe adverse events.

The analysis also takes into account those patients who developed symptomatic CHF (20 (1.19%) patients in the trastuzumab arm, 0 patients in the placebo arm). It is assumed that all patients with symptomatic CHF would discontinue treatment. Note that a disutility is not associated with symptomatic CHF (only severe CHF).

Severe adverse events are also associated with an increased risk of mortality. The HERA trial reported a rate of 0.4% fatal adverse events for patients receiving trastuzumab (6 deaths), compared with 0.2% for placebo (3 deaths). There were 117 serious adverse events for patients receiving trastuzumab, approximately 5.1% of these events were fatal, compared with 3.7% for placebo patients (i.e. increase in mortality of 1.4%).

The analysis assumed that all severe adverse events result in discontinuation of treatment, which appears to be consistent with withdrawal rates reported in the clinical trial.

The analysis assumes that patients who withdraw from treatment in the first 6 months do not receive the additional benefits of trastuzumab. Patients who withdraw after 6 months of treatment receive half the additional benefits associated with trastuzumab in terms of reduced relapse rates.

The analysis also assumes that the cardiac events are reversible (i.e. patients do not continue to receive a lower quality of life for their remaining life years)[5]. This is an optimistic assumption, favouring trastuzumab.

Local and Regional Relapse

The probability of a local relapse in the first 6 months was 1.0% for patients administered trastuzumab, compared with 2.2% for placebo patients. The probability of a regional relapse was 0.6% for patients administered trastuzumab, and 0.8% for placebo patients.

The analysis assumes that patients that remain in remission have a reduced risk of relapse over time. The Early Breast Cancer Trialists' Collaborative Group reported that patients experience 100% risk between years zero to four, 64% of the baseline risk between years five to nine, and 41% of the initial relapse risk for the remainder of their lives [20]. This reduction in risk over time applies to both local/regional relapses and metastatic relapses.

The majority of patients have previously had a mastectomy or breast-conserving surgery, hence patients who then develop a local/regional relapse are likely to have a lumpectomy to remove the lesion, followed by radiotherapy and/or a further 6 months of chemotherapy.

The risk of these patients developing metastatic breast cancer is assumed to be 4.4 times higher than disease-free patients (those in the remission arm).

It is assumed that patients who have a local relapse do not have an increased risk of mortality, as the majority are able to be treated effectively (patients who don't respond to treatment are likely to develop advanced breast cancer prior to death).

Contralateral Relapse

The probability of a contralateral relapse was 0.4% in both treatment arms. These patients are likely to undergo surgery (mastectomy or breast-conserving surgery), followed by radiotherapy and/or chemotherapy.

Metastatic Relapse

The probability of a distant relapse was 5.0% for patients administered trastuzumab, compared with 9.1% for placebo patients. Patients are likely to receive chemotherapy or trastuzumab under Special Authority for HER-2 positive patients.

Patients who develop metastatic disease are likely to enter one of four health states – death, stable, response, or progressive disease. The transitional probabilities were based on a key clinical trial with the following treatment regimens [21]:

- chemotherapy plus trastuzumab;
- either type of chemotherapy alone;
- anthracycline, cyclophosphamide plus trastuzumab;
- anthracycline plus cyclophosphamide;

[5] In the B-31 trial, of the 31 patients in the trastuzumab group who developed congestive heart failure, 27 were followed for at least 6 months after the onset of heart failure, and only 1 reported persistent symptoms of heart failure at the most recent follow-up visit.

- paclitaxel plus trastuzumab;
- paclitaxel alone.

The transitional probabilities were calculated using a weighted average of trastuzumab regimes (20% of patients are assumed to be HER-2 positive), and other treatment regimes (80% of patients).

In the key trial on trastuzumab in metastatic breast cancer (Slamon et al.), approximately 34.0% of patients responded to treatment [21]. Of these patients, 6% had a total response (defined as the disappearance of all tumour), and hence moved to the remission health state. The remainder of patients had a partial response (defined as a decrease of more than 50% in the dimensions of all measurable lesions). The median duration of response was 6.5 months, hence it was assumed that patients who had a partial response remained in this health state.

Metastatic breast cancer is also associated with an increased risk of death (weighted average mortality rate of 12.1% after 6 months) [21].

The probability of disease progression after 6 months was 51.4% [21], upon which patients receive palliative care (mortality rate of 5% per month, or 25.5% after 6 months).

Mortality

The general (non-breast cancer) mortality rate was based on the New Zealand age-specific mortality rates for women.

These rates were adjusted for the additional mortality associated with metastatic breast cancer, end-stage breast cancer, and severe adverse events. These rate-adjustments were independent of age.

Quality of Life

Quality of life was estimated using EQ-5D New Zealand weights [24], informed in part by Australian Burden of Disease Study (ABDS) disability weights [25].

Utility values were estimated for the following health states:

- early-stage breast cancer in remission;
- local/contralateral relapse;
- distant relapse;
- palliative care;
- serious infection;
- cardiac toxicity (includes severe heart failure); and
- other serious adverse event

These utility values were estimated using descriptors of breast cancer health states, derived by oncologists [source: supplier analysis], with modifications, to map to EQ-5D generic health states. These states were agreed to iteratively by consensus[6]. NZ tariff-2 EQ-5D weights [24] were then applied to the generic health states to derive QoL scores. A similar process was used for adverse health states (infection, cardiac toxicity etc.)

Utility values assumed that patients that have a serious infection have a reduced quality of life for approximately one month, starting with severe disutility but improving to remission-state quality of life by the beginning of the second month. Patients that develop severe heart failure were assumed to have a reduced quality of life for six months; this is likely to be an optimistic assumption, as it is not known for certain

[6] These were estimated by six (blinded) PHARMAC clinical and analyst staff members with knowledge of the disease. The initial blinded results were discussed, including outliers, rates and timeframes, and then consensus was gained iteratively.

whether the severe heart failure is reversible – patients may continue to have a reduced quality of life for the remainder of their life years.
Cardiac toxicity included severe heart failure, which was used as a proxy definition when defining health states for all serious cardiac toxic events reported in HERA [1]; severe heart failure was defined as an initial grade of NYHA class III or IV (symptoms with light or no exertion), as in HERA [1], but then symptoms improving with treatment over time.

As for serious infection, patients who experience other serious adverse events (details of these events were not specified in the HERA trial) were assumed to have a reduced quality of life for one month.

Using these methods and assumptions derived the following quality of life scores (utilities) used in the model:

Disease state	EQ5D state	EQ5D description
Breast cancer		
Disease free / in remission, > 5 years	11111	No problems walking; no problems with self care; no problems with performing usual activities; no pain or discomfort; not anxious or depressed.
Disease free / in remission, < 5 years	1111(1-2)	No problems walking; no problems with self care; no problems with performing usual activities; no pain or discomfort; between not and moderately anxious or depressed.
Local/regional relapse	1122(2-3)	No problems walking; no problems with self care; some problems with performing usual activities; moderate pain or discomfort; between moderately and extremely anxious or depressed.
Contralateral primary	1122(2-3)	No problems walking; no problems with self care; some problems with performing usual activities; moderate pain or discomfort; between moderately and extremely anxious or depressed.
Metastatic cancer	22(2-3)(2-3)3	Some problems walking about; some problems washing or dressing self; between some problems and unable to perform usual activities; between moderate and extreme pain or discomfort; extremely anxious or depressed.
Terminal phase (prior to death)	3(2-3)3(2-3)3	Confined to bed; between some problems and unable to wash or dress self; unable to perform usual activities; between moderate extreme pain or discomfort; extremely anxious or depressed.
Trastuzumab adverse effects		
Serious infection e.g. septicaemia (initial)	33333	Initially moribund – confined to bed; unable to wash or dress self; unable to perform usual activities; extreme pain or discomfort; extremely anxious or depressed. This state then improves over one month, becoming equivalent to the disease-free remission state by month two.
Cardiac toxicity including severe CHF (initially NYHA classes III and IV)	21221	Some problems walking about; no problems with self care; some problems with performing usual activities; moderate pain or discomfort; moderately anxious or depressed. This state then improves with treatment.
Other serious adverse event (initial)	21221	Initially unwell – some problems walking about; no problems with self care; some problems with performing usual activities; moderate pain or discomfort; moderately anxious or depressed. This state then improves over one month, becoming equivalent to the disease-free remission state by month two.

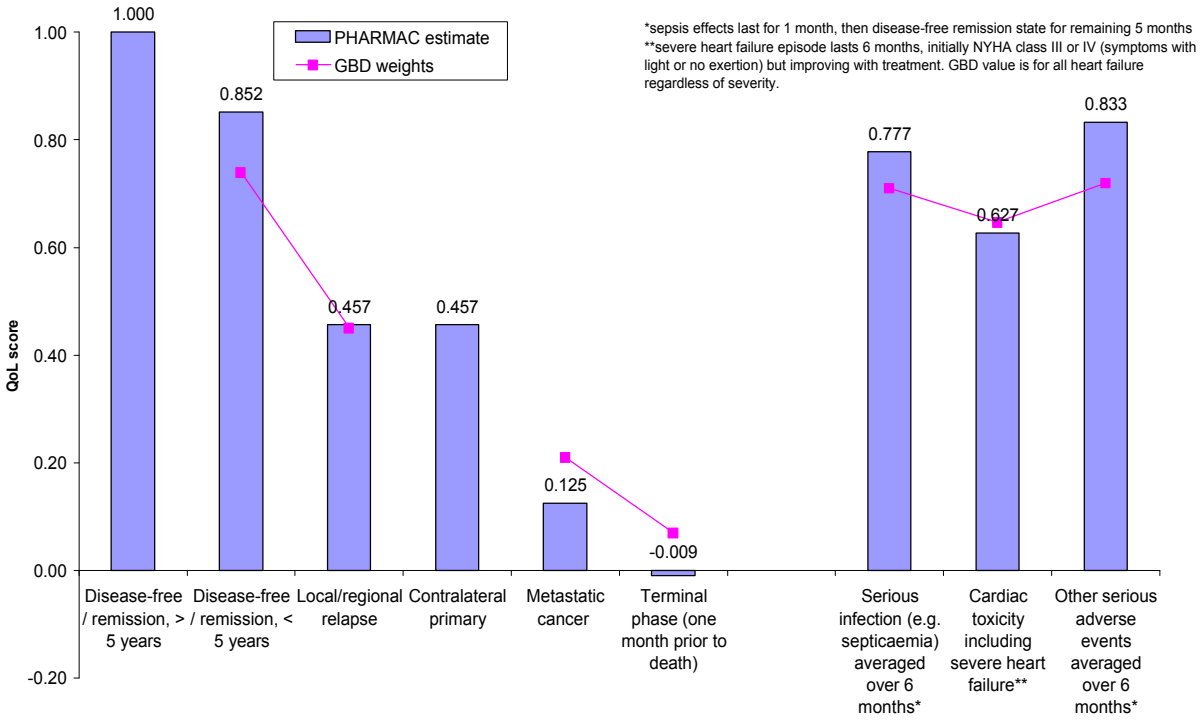
The model's utilities are generally similar to the utilities derived from ABDS disability weights (which incorporated both Global Burden of Disease (GBD) and Dutch disability weights [26,27]:

	PHARMAC		GBD weights
	EQ5D state	QoL score	QoL score
Disease-free / remission, > 5 years	11111	**1.00**	
Disease-free / remission, < 5 years	1111(1-2)	**0.85**	0.74
Local/regional relapse	1122(2-3)	**0.46**	0.45
Contralateral primary	1122(2-3)	**0.46**	
Metastatic cancer	22(2-3)(2-3)3	**0.13**	0.21
Terminal phase (one month prior to death)	3(2-3)3(2-3)3	**-0.01**	0.07
Serious infection (e.g. septicaemia) averaged over 6 months*	33333	**0.78**	0.71
Cardiac toxicity including severe heart failure**	21221	**0.63**	0.65
Other serious adverse events averaged over 6 months*	21221	**0.83**	0.72

*average over 6 months, where sepsis etc. effects last for 1 month, then disease-free remission state for remaining 5 months

**severe heart failure episode lasts 6 months, initially NYHA class III or IV (symptoms with light or no exertion) but improving with treatment. GBD value is for all heart failure regardless of severity.

Quality of life values for breast cancer and Herceptin adverse effects



Cost Information

Pharmaceutical and Administration Costs

Pre-Administration Tests
Prior to receiving trastuzumab, cardiac risk should be excluded. Patients in the HERA trial had an echocardiography to confirm normal left ventricular ejection fraction (LVEF). The cost of an echocardiogram is approximately $250, and cost of initial cardiology outpatient appointment is $255 [18].

Cost of Trastuzumab
Trastuzumab is administered by intravenous infusion over a period of 90 minutes. The initial loading dose is 8 mg/kg, followed by maintenance doses of 6 mg/kg every three weeks (based on weight and age distribution of New Zealand women).

A patient is assumed to receive one loading dose and 17 maintenance doses for completion of therapy (loading dose and 8 in first six months and 9 in remaining six months). The total yearly dose is 110 mg/kg. Note that this assumes no drug wastage.

Table 13: Cost of Trastuzumab

Description	Cost per unit
Trastuzumab cost per mg (current Pharmaceutical Schedule price)	8.81
Trastuzumab loading dose 8mg/kg	$5,074.56 (based on weight of 72 kg)
Trastuzumab maintenance dose 6mg/kg,	$3,805.92 (based on weight of 72 kg)

Note that the CUA was based on a lower proposed price of trastuzumab (confidential information).

Outpatient Administration Cost
Patients need to be observed for at least six hours following the first infusion, and at least two hours for subsequent infusions. It is likely that a specialist will supervise the infusion (approximately 15 minutes of specialist time), and a nurse will administer treatment and monitor the patient. Based on a nursing cost of $23 per hour and specialist cost of $90 per hour for follow-up, the minimum cost associated with administering trastuzumab is $195 for the first administration, and $103 for subsequent infusions.

The cost of bed utilisation during and after the infusion is still being investigated. It is unclear how much time patients will need in a bed as opposed to being supervised in a day room.

Until further information becomes available, the base-case administration cost is assumed to be $100 per infusion ($850 per cycle) with sensitivity analysis using a range of $0 to $5000.

Cardiac Risk Monitoring
Patients receiving trastuzumab will also receive ongoing monitoring for signs of cardiac toxicity. In the HERA trial, patients were assessed at months 0, 3 and 6; and then every 6 months thereafter for 5 years. This included a cardiac questionnaire, physical examination, electrocardiogram, and echocardiography or MUGA scanning. The analysis assumes patients will be assessed at these points of time while receiving trastuzumab (i.e. 12 months of treatment).

The cost of specialist follow-up appointments is approximately $90 ($80-$100), cost of echocardiogram is $255, and cost of an electrocardiogram (ECG) is $62.

Table 14: Cost of Cardiac Risk Monitoring

Description	Cost per unit
Initial nurse infusion (7.5 hours)	$23 per hour
Subsequent nurse infusions (3.5 hours)	$23 per hour
Specialist supervision (15 min)	$50
Initial cardiac risk assessment – echocardiogram	$250
Initial cardiac risk assessment – cardiologist	$255 per appointment
Cardiologist follow-up	$90 per appointment
Echocardiogram	$250
ECG	$62

Other Pharmaceutical Costs

The cost of tamoxifen is $32.36 per year, and the cost of anastrozole is approximately $3,000 per year. It is assumed that 80% of hormone-receptor positive patients would be administered tamoxifen, and 20% administered anastrozole. This cost is incurred for the first 5 years of the comparator treatment arm, and for 4 years after patients receive trastuzumab. The dispensing fee is $5.16, and pharmacy mark-up is 3%.

Outpatient Costs for Disease-Free Patients

Patients who are relapse-free still require regular follow-up and clinical assessments (history and physical examination), as follows:

- year 1 – every 3 months;
- year 2-5 – every 6 months;
- year 6 -10 – yearly.

The cost per follow-up is likely to be $80-$100 (average of $90).

It is also recommended that patients receive a mammography every year (cost of approximately $140, source: Sovereign Health).

The outpatient costs per year following chemotherapy are as follows:

- year 1 - $500
- years 2-5 - $320
- years 6-10 - $230
- >10 years - $140

Cost of Local Relapse

Patients who have a local relapse have previously had a mastectomy or breast-conserving surgery, hence are likely to receive a lumpectomy (removal of the lesion) followed by chemotherapy and/or radiotherapy.

The cost of pre-surgery and post-surgery consultations with an oncologist is included in the analysis. The cost of an outpatient consultation is $120-$255 (average $200), and cost of follow-up consultations is $80-$100 (average $90) (source: private hospital).

The cost of a lumpectomy was estimated using DRG code J07A (minor procedures for malignant breast conditions). The estimated price is $2,279.16.

Approximately 81% of patients that have local excisions receive radiotherapy [19].

Patients may also receive a further 6 cycles of chemotherapy (fluorouracil, doxorubicin, oral or intravenous cyclophosphamide).

The costs associated with a local breast cancer relapse are outlined in the table below:

Table 15: Cost of Local Relapse

Treatment	Cost	Proportion of Patients	Total Cost
Initial Oncologist consultation	$200	1	$200
Lumpectomy	$2,279	1	$2,279
Post-surgery consultation	$90	1	$90
Radiotherapy	$6,250	0.81	$5,125
Chemotherapy (FAC)	$677.82	0.5	$338.91
TOTAL COST			**$8,033**

Cost of Contralateral Breast Cancer

Patients who have contralateral breast cancer are likely to receive either one or a combination of the following treatments:

- mastectomy;
- breast-conserving surgery;
- chemotherapy;
- radiotherapy.

Based on data from the Auckland Breast Cancer Register (2000-2002), 55.8% of patients with invasive breast cancer had a mastectomy and 44.2% of patients had breast-conserving treatment [19]. The average cost of a breast cancer surgery was based on DRG J06A (major procedures for malignant breast conditions).

Of those who received breast-conserving treatment, 81.3% received radiotherapy, compared to 35.0% of patients who had a mastectomy (overall 76.8% of patients had radiotherapy). The cost of radiotherapy is based on 5 sessions per week over 5 weeks, at a cost of $250 per session (source: Ministry of Health).

The cost of breast reconstruction following a mastectomy was included in the analysis. In the Auckland Breast Cancer Register (2000-2002), 18.4% of patients treated by mastectomy also had breast reconstruction [15]. However, this number does not include those patients on the waiting list for reconstruction. An Australian study reported that up to 50% of patients had breast reconstruction following a mastectomy [20]. The analysis therefore assumes that on average approximately 30% of patients have breast reconstruction following mastectomy. The cost of breast reconstruction was based on DRG J14Z (major breast reconstructions).

Patients who have a mastectomy can also claim for breast prosthesis subsidy (source: Ministry of Health). It is assumed that patients who do not have breast reconstruction following a mastectomy will claim for breast prosthesis.

The cost of pre-surgery and post-surgery consultations with an oncologist was included in the analysis. The cost of an outpatient consultation is $120-$250 (average $200), and cost of follow-up consultations is $80-$100 (average $90) (source: private hospital).

Patients may also receive a further 6 cycles of chemotherapy (fluorouracil, doxorubicin, oral or intravenous cyclophosphamide).

Patients are likely to receive further hormonal treatment once in remission.

The costs associated with contralateral breast cancer are outlined in Table 16.

Table 16: Cost of Contralateral Breast Cancer

Treatment	Cost	Proportion of Patients	Total Cost
Oncologist consultation	$200	1	$200
Surgery	$4,806	1	$4,806
Breast reconstruction following mastectomy	$6,180	0.3	$1,854
Breast prosthesis subsidy for patients undergone mastectomy	$600	0.5	$180
Post-surgery consultation	$90	1	$90
Radiotherapy	$6,250	0.768	$4,800
Chemotherapy (FAC)	677.82	0.5	$339
TOTAL COST	**$18,804**		**$12,269**

Cost of Distant Relapse

The treatment of metastatic breast cancer is mainly medical. The goals of chemotherapy are mainly palliative and include control of symptoms, control of disease progression, and prolongation of life.

It is assumed that patients' with HER2 positive disease will receive trastuzumab, providing they have low cardiovascular risk. Research undertaken by Roche from 10 New Zealand oncologists indicated that approximately 62% of patients would receive trastuzumab for first-line metastatic cancer. It is assumed that the remainder patients receive chemotherapy (fluorouracil, doxorubicin, oral or intravenous cyclophosphamide).

Trastuzumab is administered at a dose of 4 mg/kg for the initial dose, and 2 mg/kg every week thereafter until disease progression, upon which treatment is discontinued. The cost of the loading dose is $2,537.28, and cost of subsequent doses is $1,268.64. The cost of trastuzumab per 6 months is therefore $34,253.28. The cost of administering treatment and monitoring patients (including assessment of cardiac risk) is estimated to be $3,960 per 6 months of treatment.

These costs are outlined in the table below.

Table 17: Cost of Trastuzumab for Distant Relapse

Description	Cost per unit	Cost per 6 months
Trastuzumab	$8.81 per mg	$34,253
Nurse infusion (3.5 hrs per wk)	$23 per hour	$2,093
Specialist supervision	$50 per visit	$1,300
Cardiologist appointment	$255 per appointment	$255
Echocardiogram	$250	$250
ECG	$62	$62
TOTAL COST		**$38,213**

Patients are also likely to receive treatment with a taxane, such as docetaxel. Docetaxel is infused over 1 hour every 3 weeks. The recommended dosage of docetaxel when used as adjuvant treatment is 75 mg/m^2, administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2.

The cost of docetaxel is $20.63 per mg from 80mg vial. The average patient is assumed to have a skin area of 1.7 m^2 .The cost per cycle of docetaxel is therefore $2,630.33. The cost of 50mg injection of doxorubicin is $49.95, hence the cost per cycle is $84.92. The cost of cyclophosphamide 1g is $21.50, hence the cost per cycle is $18.275. The total cost of treatment over six cycles is approximately $16,000, resulting in a total cost for treatment of metastatic disease with trastuzumab and chemotherapy of approximately **$54,213.**

Approximately 38% of patients will be administered standard chemotherapy - fluorouracil (500mg/m^2), doxorubicin (50 mg/m^2), oral or intravenous cyclophosphamide (500 mg/m^2). It takes approximately one hour to administer treatment, which is assumed to be administered by a nurse (cost of $23 per hour). The total cost of chemotherapy is approximately $701.

It is also assumed that all patients will have one hospitalisation every 6 months, at an average cost of $2,000 (volume-weighted average price of hospitalisation due to metastatic breast cancer - DRG62A-C).

Table 18: Total Cost of Distant Relapse

Description	Cost per 6 months	Proportion of Patients	Total Cost
Trastuzumab plus chemotherapy	$54,213	0.62	$33,612.06
Chemotherapy alone	$701	0.38	$266.38
Hospital	$2,000	1	$2,000
TOTAL COST			**$35,878**

Cost of Terminal Care

The cost of palliative care includes either:

- cost per day of staying in a hospice (70% of patients – NZ Cancer control strategy) - $560 (source: Mary Potter Hospice) - $16,800 per month;
- cost of palliative care in hospital - $350 per night ('hotel' cost of staying in hospital) - $10,500 per month;
- community care - $800 per month (8 nurse visits and/or GP visit plus drug treatment).

The analysis assumes that 70% of patients have their last month of life either in hospital or a hospice (35% in hospital, 35% in hospice), and 30% in the community, resulting in a cost of approximately $9,795. This cost was modelled as a transitional cost prior to death.

The months prior to death are likely to be in the community (approximately 70%), at a cost of $4,800 per six months, or in hospital/hospice (approximately 30%) at a cost of $81,900 per 6 months; resulting in a total average cost per six months of $27,930.

As the half-cycle correction assumes that death occurs in the middle of the cycle, this means that patients are effectively staying for either 3 months or 9 months in this state.

Both the external reviewer as well as PTAC noted that the cost of terminal care may be overstated from the assumptions around resource use (hence favouring trastuzumab).

Cost of Serious Infection

The HERA trial did not specify the type of serious infections that patients developed in the trial. The analysis therefore assumes that the effects of infection were equivalent to the effects of any type of reticuloendothelial and immunity disorder. The cost of hospitalisation was therefore based on DRG Q60B (reticuloendothelial and immunity disorder without catastrophic or severe complications, with malignancy). The average cost of hospitalisation is estimated to be $4,359.

Cost of Cardiac Toxicity

The cost of hospitalisation due to cardiac toxicity (including severe heart failure NYHA classes III and IV) was based on DRG F62B (heart failure without catastrophic complications). The average cost per hospitalisation was estimated as $2,983. The outpatient cost of managing a patient with congestive heart failure for 6 months is approximately $1,198. Therefore the total cost of cardiac toxicity is approximately $4,181.

Cost of Other Serious Adverse Event

As it is not known what these serious adverse events were, an average one-off cost of $4,000 was attributed to these events.

Results of CUA model

The preliminary results of the CUA indicate that the incremental cost per quality-adjusted life year (QALY) of one-year's trastuzumab treatment compared with standard treatment for patients with early HER-2 positive breast cancer is approximately **$70,000-$80,000** (12.5 to 14.3 QALY's gained per $1 million invested).

Sensitivity analyses

An initial one-way sensitivity analysis was conducted, using the then current input values, to identify which variables would significantly influence the model results if varied:

Variable	Base-Case Analysis	Sensitivity Analysis	QALY's gained per $ million	Cost per QALY
Base Case			**14.28**	**$70,000**
Price of trastuzumab	-	30% reduction	21.51	$46,000
Price of trastuzumab	-	50% reduction	32.46	$31,000
Duration of benefit	4 years	2 years	7.86	$127,000
Risk of Relapse in both treatment arms		50% reduction	8.84	$113,000
Duration of benefit and price cut 30%	4 years, current price	2 years, 30% price cut	11.24	$89,000
Duration of benefit	4 years	Lifetime	40.98	$24,000
Discount rate	8.0%	0.0%	27.09	$40,000
Discount rate	8.0%	3.5%	21.74	$46,000
Cost of palliative care	-	50% increase	15.23	$66,000
All adjuvant costs (excluding pharmaceutical cost)	-	20% increase	14.92	$67,000
All adjuvant costs	-	20% reduction	14.38	$70,000
Roche's utility values	-		13.80	$73,000
Treatment duration	1 year	2 years	7.29	$144,000

As can be seen from above, the results are very sensitive to the assumed duration of relative benefit from trastuzumab. Assuming a treatment benefit of only two years (as per the published data) the cost per QALY is estimated to increase to $126,000. On the other hand if the benefit was persisting for a lifetime, the estimated cost per QALY would fall to $24,000. Other key drivers are the cost of trastuzumab (which in turn is significantly influenced by dose, weight and treatment duration) and the discount rate (due to high initial costs and potential lifetime benefits).

After updating the model following the comments from PTAC and the external reviewer, further sensitivity analysis (univariate and multivariate), particularly around treatment length and benefit (time to recurrence of breast cancer) was conducted with the results as below:

Variable	Cost per QALY
Base Case	$73,000
Lifetime duration of breast cancer risk reduction.	$26,500
FinHer dose, 4 yr duration of breast cancer risk reduction.	$12,318
FinHer dose 2yr duration of breast cancer risk reduction	$29,240
4 yr duration of breast cancer risk reduction +4 yr half benefit	$54,302
2 yr benefit +lifetime half	$52,649
2 yr benefit +6 yr half benefit	$67,507

Discussion and Further Information

FinHer – 9-weeks of trastuzumab in association with adjuvant chemotherapy

The FinHer trial [36] assessed the effects of a 9-week adjuvant regime of trastuzumab administered before cardiotoxic chemotherapy. Published in February 2006, the results of 3-year recurrence-free survival suggested prima facie that the 9-week trastuzumab regime had similar reductions in disease events as the one-year regime used in the HERA trial [1]. Information from FinHer was not included in the initial draft CUA as this treatment regime differs from the Medsafe approved regime and the current submission for funding.

FinHer was an open-label RCT that included a comparison of a 9-week adjuvant trastuzumab regime, following on from docetaxel or vinorelbine, with no such adjuvant treatment (i.e. docetaxel or vinorelbine alone). For 232 women followed-up for a median of 36 months, women who received trastuzumab had fewer distant recurrences of breast cancer than those in the control group (hazard ratio = 0.29, or an ARR 5.5% at one year's follow up, 8.5% at 2 years 12.8% at 3 years). Overall survival tended to be better (hazard ratio for death 0.41) – this didn't quite reach statistical significance (note that patient numbers were small). There were no differences in cardiac outcomes between treatment arms.

PTAC considered the FinHer study at its May 2006 meeting. The committee noted that the trastuzumab treatment arms of the FinHer trial were relatively small (232 patients) and that the trial might not have been sensitive enough to reliably detect cardiac toxicity. However, the committee considered that, given the proposed molecular mechanisms of trastuzumab and anthracycline cardiotoxicity, the treatment sequence used in the FinHer study (i.e. trastuzumab prior to anthracycline) might have substantially reduced the risk of developing cardiac toxicity. PTAC considered that the FinHer Study cast significant doubt regarding the optimal duration and timing of trastuzumab treatment.

Further details of PTAC's assessment of FinHer can be found in Appendix Two.

The following table and graphs show the characteristics and results over time of the FinHer and HERA trials, where relative reductions in disease-free events were of similar magnitude but the FinHer (9 week) regime costs 1/5th that of the HERA (1 year) regime.

Table 19: HERA and FinHer trials

	HERA Trial	FinHer Trial
Study design	Open label RCT	Open label RCT
Patient Numbers	Observation – 1,693 1 year trastuzumab – 1,694 2 year trastuzumab – 1,694	Observation: Trastuzumab: Docetaxel – 58 Docetaxel + trastuzumab - 54 Vinorelbine – 58 Vinorelbine + trastuzumab - 62
Intervention	1 loading dose (8mg/kg) trastuzumab, then 6mg/kg every 3 weeks for one year or two years (17 or 35 infusions, respectively).	9 trastuzumab infusions at 1 week intervals. First dose 4mg/kg (90min infusion), remaining doses 2mg/kg (30 min infusion)

Comparator(s)	Observation	Docetaxel or vinorelbine plus FEC (5-fluorouracil, epirubicin and cyclophosphamide) treatment regimens without trastuzumab.
Length of follow-up	One year of trastuzumab: 12 months (published data[7]), 23 months (unpublished[8], only selected information available). Two years of trastuzumab: no information available for this study arm.	Median 36 months (20-55)
Drug cost ($NZ)	1 year - $69,000 (total dose = 110mg/kg) 2 year - $137,000 (total dose = 218mg/kg)	9 weeks = $12,600 (total dose = 20mg/kg)
Hospital cost ($NZ)	1 year - $3,500 2 year - $7,300	9 weeks = $1,800
Important clinical outcomes	Lower disease recurrence (ARR 5.5% at one year follow up, ARR 6.1% at two years follow up (unpublished)) in patients treated with one year of trastuzumab. No statistically significant difference in overall survival between the two arms at one year (published information). The 23 month follow-up evidence suggests that one year trastuzumab does translate into improved overall survival. Increased risk of cardiotoxicity in patients receiving trastuzumab.	The women who received trastuzumab had fewer distant recurrences of cancer than those in the control group (hazard ratio = 0.29), or an ARR 5.5% at one year's follow up, 8.5% at 2 years 12.8% at 3 years) Overall survival tended to be better (hazard ratio for death 0.41) – this didn't quite reach statistical significance (note small patient numbers). No difference in cardiac outcomes between treatment arms. It has been suggested that decreases in LVEF and heart failure (reported in HERA) may be the result of receiving the drug for a longer period of time, or the sequence of drug administration.

[7] **Published data:** refers to results that have been reported in journals (and therefore have been subject to a peer review process). The published papers referred to in this document (HERA one year follow-up, Romond and FinHer), were published in the New England Journal of Medicine.

[8] Unpublished data refers to results that have been supplied to PHARMAC in a form that has not been subject to peer review. In this case, this includes extra trial data supplied to PHARMAC (that was omitted from published articles), and powerpoint presentation slides that have been presented at conferences. The unpublished results are discussed further in the final section of this report ('Important information to note')

Figure: Comparison of disease-free survival over time in HERA and FinHer trials

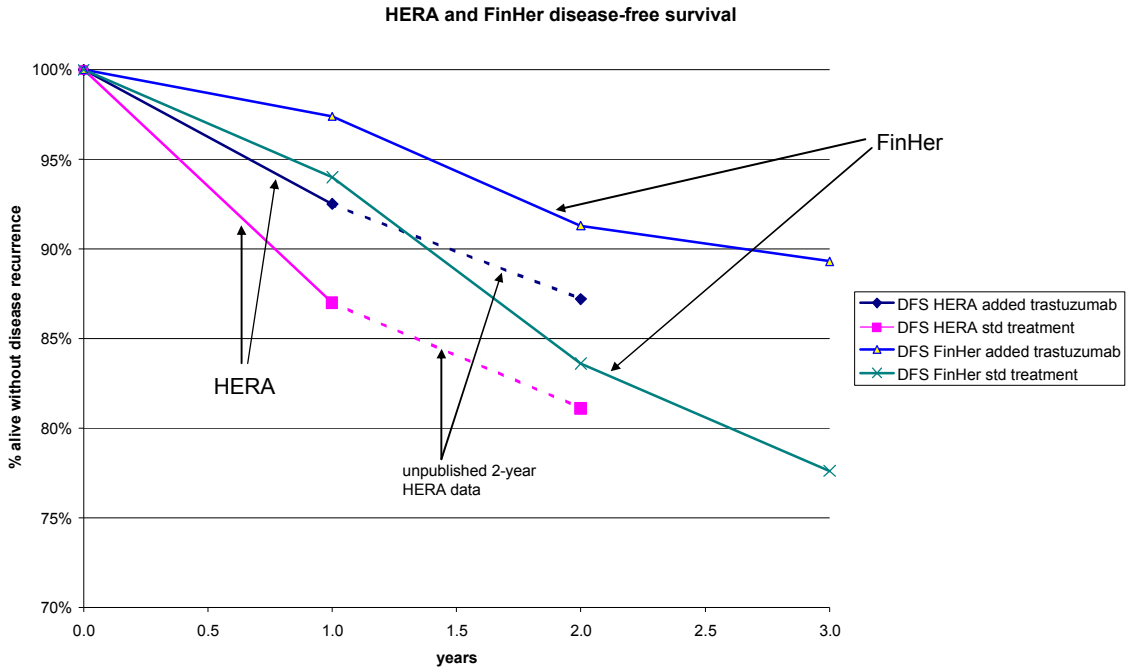
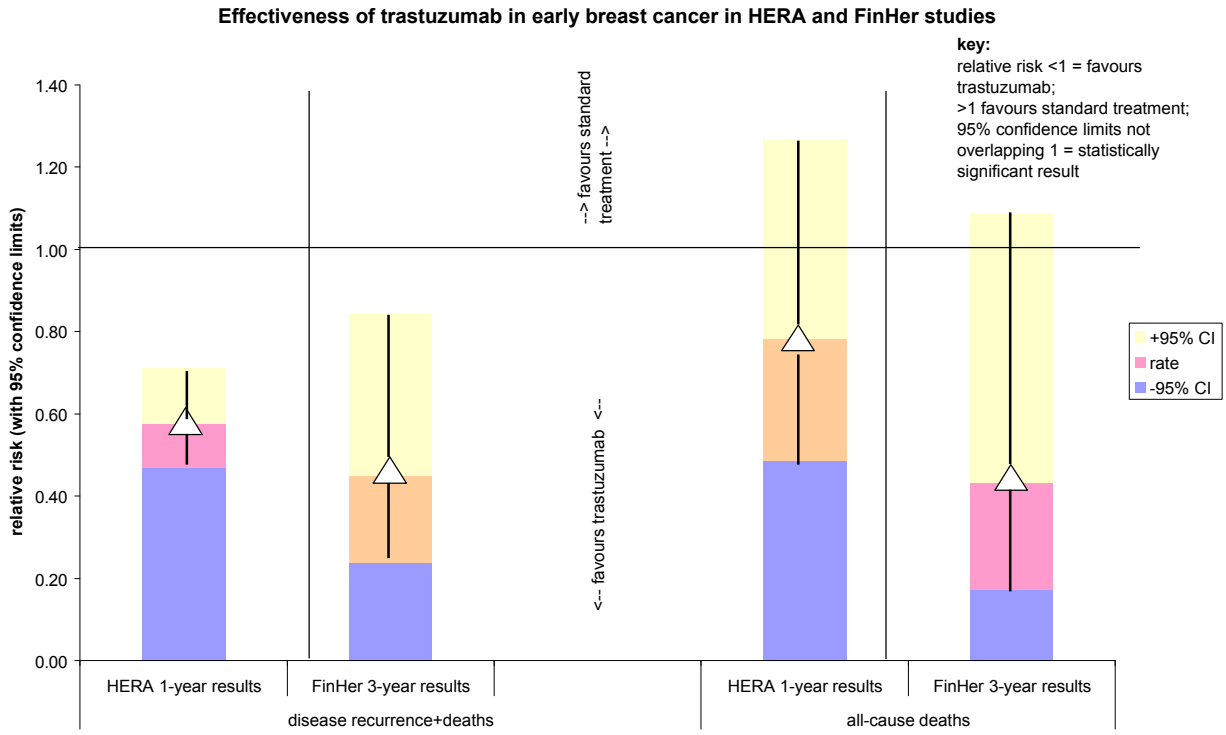


Figure: Effectiveness of Trastuzumab treatment in HERA and FinHer trials



Hence, as suggested by 3-year recurrence-free survival in FinHer, it is possible that adjuvant trastuzumab is no less effective when given for this shorter (9-week) period of time, and almost halving the costs. FinHer has generated considerable interest since its findings were presented at the San Antonio Breast Care Symposium (SABCS) in 2005,

with speculation that its shorter treatment schedule is still effective and 'may facilitate lower cost, greater patient convenience, and reduced risk of cardiotoxicity' [37].

The 9-week regime has not been considered by Medsafe and is not licensed for the early treatment of breast cancer in New Zealand.

At this stage, considering both physiological evidence and the published trial evidence available, the 9-week FinHer trastuzumab regimen appears to be arguably as effective as the 12-month HERA regimen.[9] Whilst doubt arises with FinHer's small size, nevertheless numbers were large enough to detect a statistically significant difference in recurrence-free survival between treatments, and the 3-year follow-up data published to date are of greater duration than HERA's 1-year data. The need for caution when interpreting results applies to both trials:

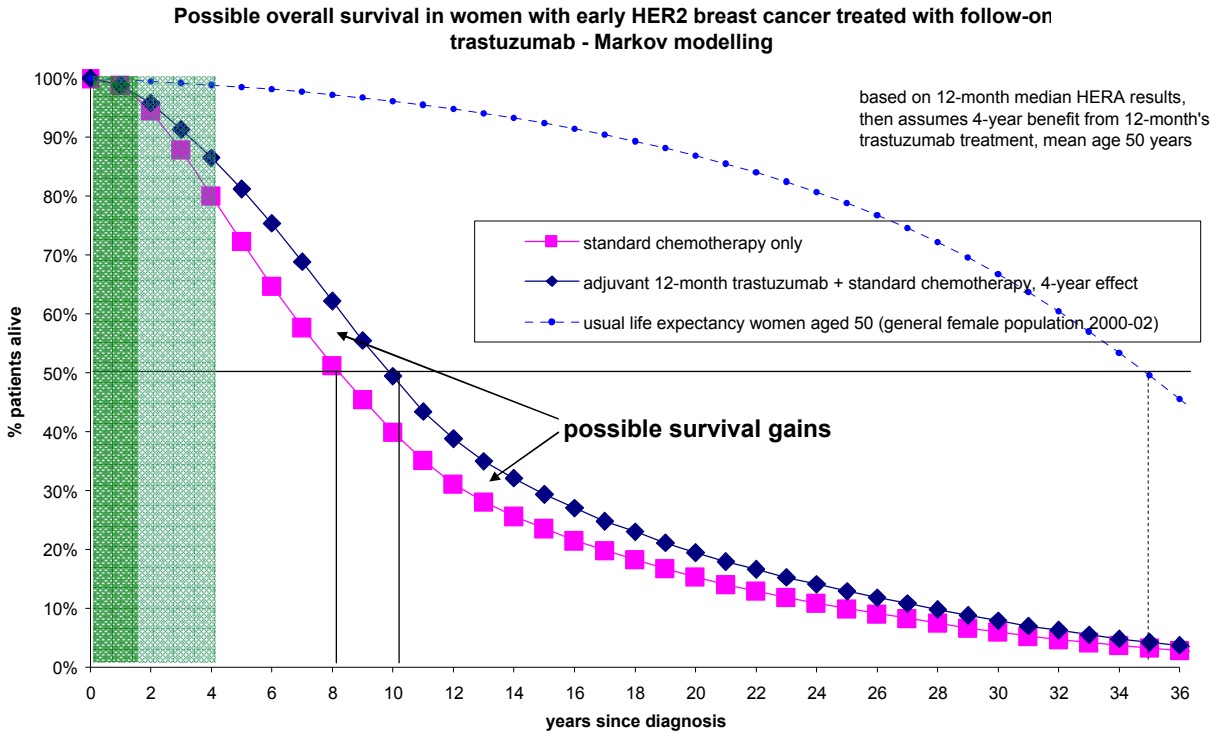
- Small patient numbers mean that FinHer may have been underpowered to detect cardiovascular toxicity. This means that results seen in clinical practice could be quite different.
- While the HERA data are numerically robust, effectiveness was shown for 1-2 years only, and there are risks extrapolating beyond that time.

ScHARR included the FinHer study in its report, but commented that 'while its results are striking, it is important that they are interpreted with caution' [37]. The authors of FinHer have also stated that 'the optimal duration of adjuvant trastuzumab therapy is not known and may be clarified only in further randomized trials' [36]. Evidence from non-inferiority or equivalence trials comparing the 9-week and one-year regimes is not available.

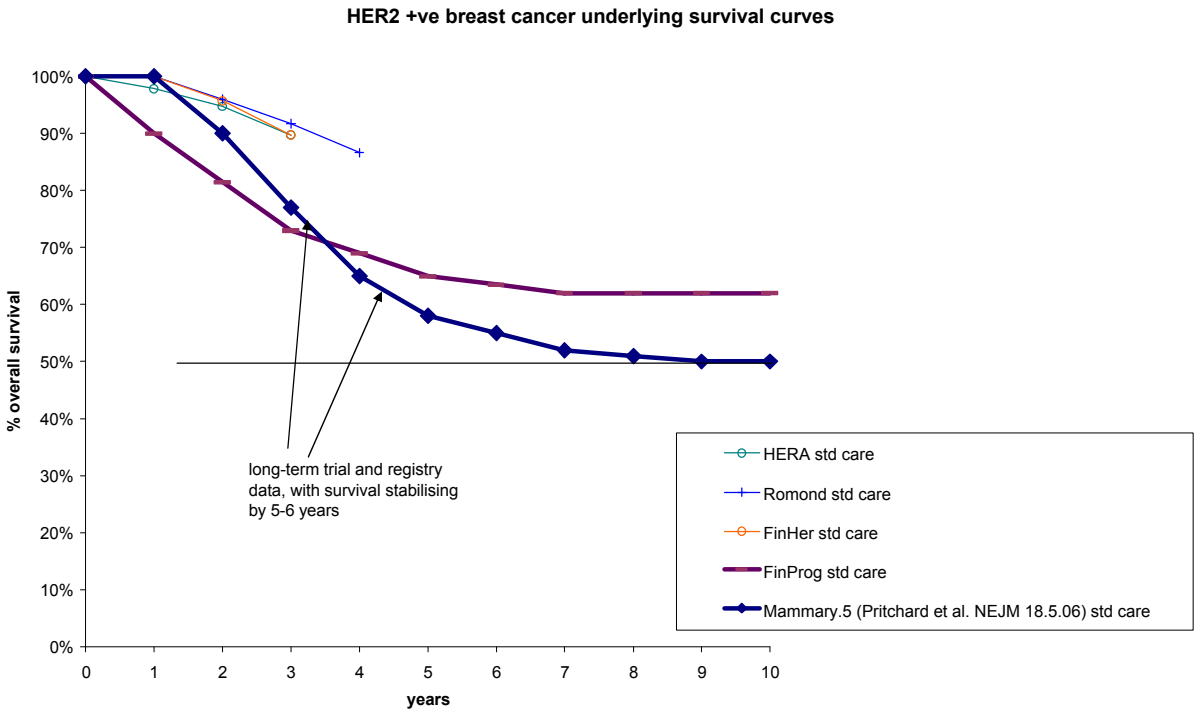
[9] ScHARR also commented that trastuzumab was not associated with cardiac adverse events in the FinHer trial, suggesting that decreases in LVEF and heart failure may be the result of receiving the drug for a shorter period of time. However, small numbers introduce the possibility of type 2 error (not detecting a true increase)

Validation of underlying survival in HER2-positive breast cancer

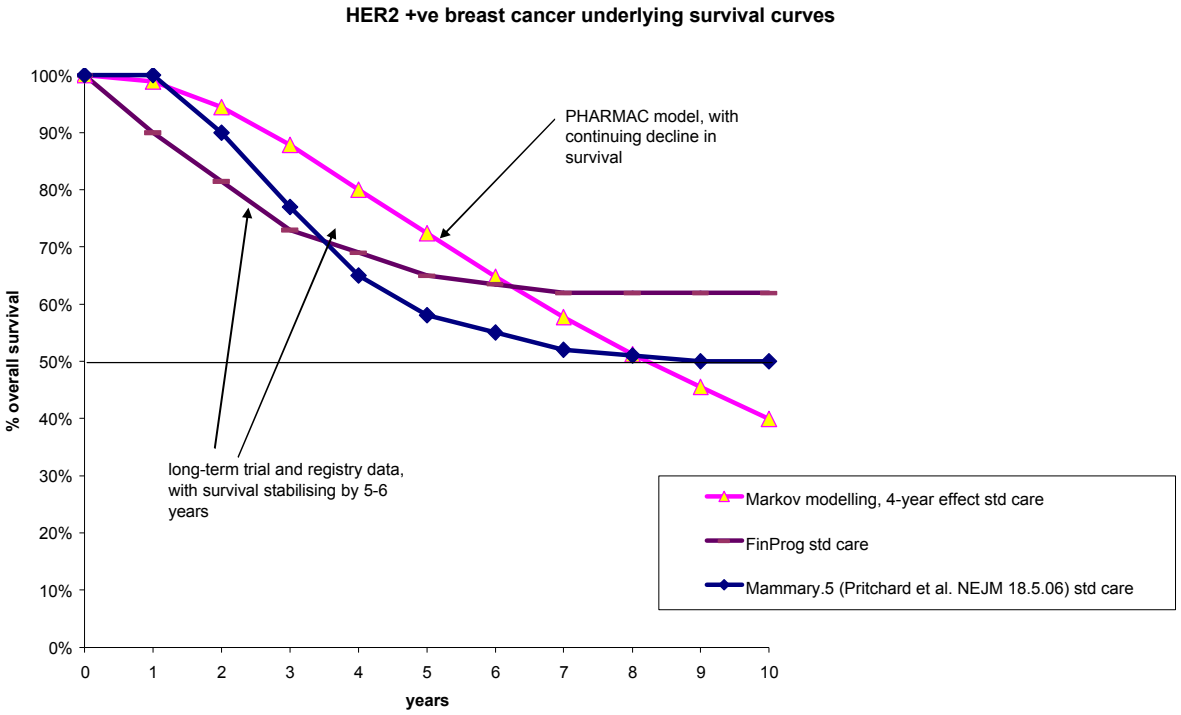
The effect of the PHARMAC model is for a persistent decline in survival with time, as seen in the following graph.



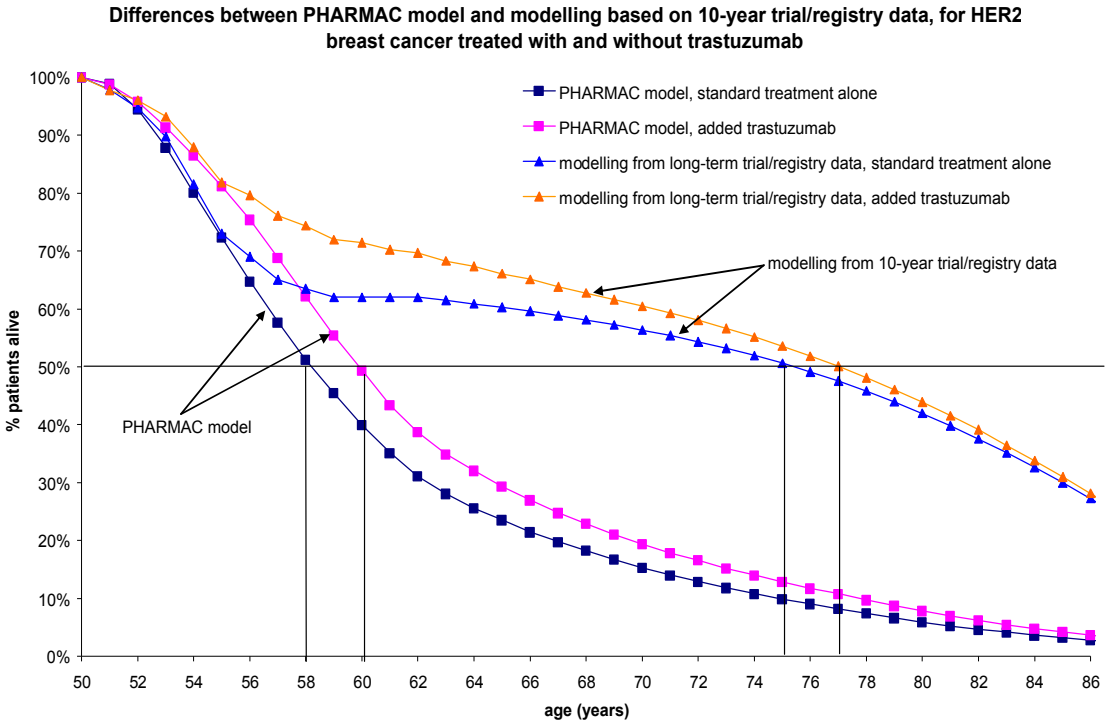
However, recently published 10-year follow-up data from a large clinical trial [33], along with available 10-year follow-up registry data from Finland [34], show survival patterns for HER2-positive breast cancer treated with current standard care, whereby survival stabilises after 5-6 years (curves 'flatten out') – similar to all breast cancers.



These patterns are distinct from the continuing decline in survival seen in Markov modelling (in the PHARMAC model, analysis undertaken by ScHARR for NICE [37], and models developed by Roche and submitted to NICE) from ongoing and cumulating culminating mortality due to a persisting (if eventually reduced) risk of breast cancer recurrence.



The graph below shows the effects on survival of disparity between PHARMAC's Markov modelling and the long-term trial and registry data, extrapolating beyond 10 years and modelling the effects of disease event reductions from trastuzumab.



Using this alternative pattern of underlying survival for early HER2 positive breast cancer not treated with trastuzumab – and the consequential shift survival for those treated with trastuzumab – would likely make trastuzumab less cost-effective than under the base case survival patterns. This is because QALY losses (and hence QALY gains) and health sector cost savings would be delayed (from the effects of discounting) when trastuzumab cost flows remain unchanged. Hence, the use of the PHARMAC model favours trastuzumab.

The ScHARR analysis

Subsequent to PHARMAC developing the above economic model, NICE (as part of developing its guidance [16]) commissioned a review of a CUA undertaken by Roche. The consequent report [37], by the University of Sheffield School of Health and Related Research (ScHARR), has been placed on the NICE website at http://www.nice.org.uk/page.aspx?o=328487 . The ScHARR report revised Roche's work and derived new estimates of cost-effectiveness.

The ScHARR report (p.94) initially estimated a revised base case of £18,500 per QALY, using a 3.5% discount rate. This was based on a number of revised assumptions, including trastuzumab being provided for all patients in the metastatic setting and no further benefit of treatment beyond five years. Other scenarios modelled on this estimate gave cost/QALYs of £16,000 to £33,000. ScHARR also concluded (pp. 9-10) that the combined effects of a number of uncertainties had the potential to increase the ICUR from Roche's base case estimate of below £5,000 to revised estimates of around £20,000 to £30,000/QALY. These uncertainties comprised:

- the long term extrapolation of the comparator arm;
- the long term benefits of trastuzumab in terms of reduction in the risk of recurrence;
- the extent to which reductions in the rate of recurrence will translate into benefits in overall survival; and
- the extent to which patients in both the comparator arm and the trastuzumab arm are likely to receive trastuzumab in the metastatic setting.

In addition, the ScHARR report considered that the addition of potential long term cardiac events could push the ICUR above £30,000/QALY, although it acknowledged that there was no long term evidence to date surrounding this issue.

Following representation from Roche (http://www.nice.org.uk/page.aspx?o=328494), ScHARR revised its base case estimate (from the £18,500 per QALY) to new estimates of £20,400 to £25,100 depending on how weekly trastuzumab was costed (http://www.nice.org.uk/page.aspx?o=328530).

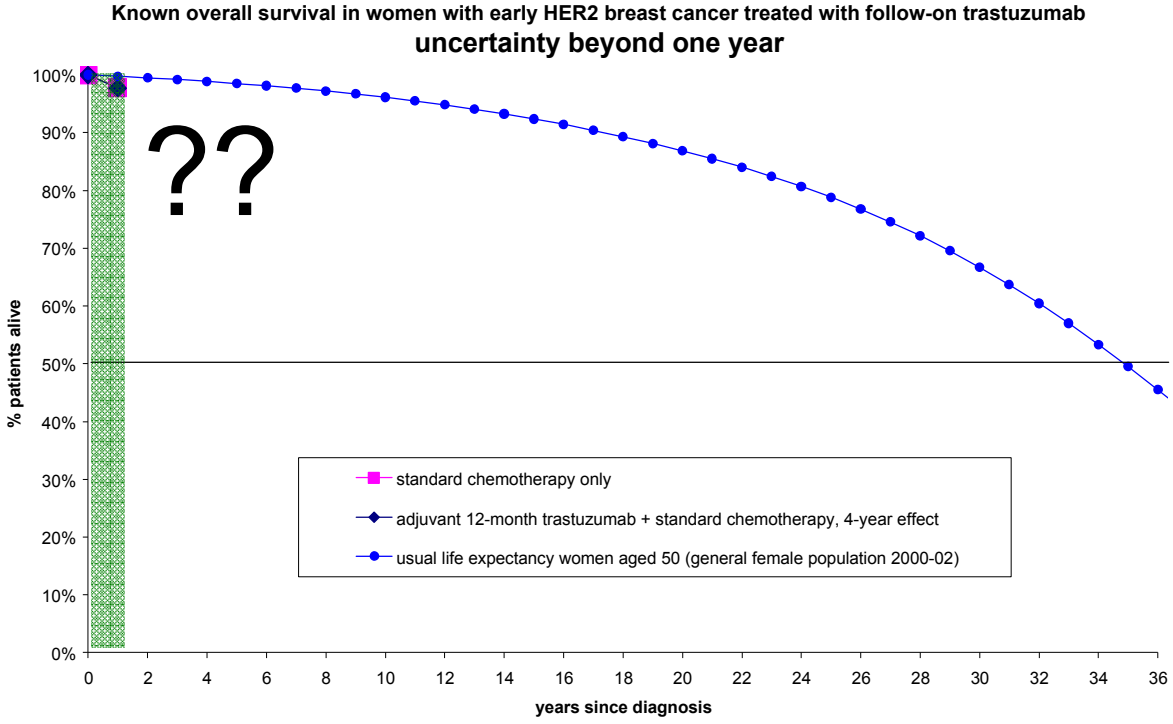
Note the Roche model was for lifetime benefit, whereas the ScHARR base case used 5 years only. This seemed to be the key driver of differences between the two. Given the absence of published evidence of long-term benefit; ScHARR's analysis assumed that one year's treatment meant a reduced risk of relapse for 5 years, with consequent later improvements in longevity.

Published analyses elsewhere

Prior to analysis by ScHARR, there was only one published economic analysis of trastuzumab in early breast cancer [30]. The results of this analysis are difficult to interpret in the New Zealand setting. Other analyses have related to advanced disease [31, 32].

Uncertainty

The key two key issues with assessing the likely cost-effectiveness of trastuzumab are the optimal duration of treatment and the likely persistence of effect. Any modelling for trastuzumab is for the rest of peoples' lives; yet for the one-year course, modelling in the main analysis is based on just one primary study that lasted 2 years [1] and two supplementary studies (for a very different regime) with four years of outcome data [2]. Patterns of disease progression beyond then are unknown.



Also, there is uncertainty with regards to the clinical evidence – where the peer-reviewed data provided to date are limited to interim analysis from one year's follow-up of an open-label, unblinded, phase III clinical trial [1], and three year's follow-up of a small similar trial using a shorter regime [36].

Given the clinical data are uncertain, it is reasonable to have a wide range of cost/QALY.

A number of questions still need to be addressed regarding trastuzumab use in early HER2-positive breast cancer. These include:

- Is there likely to be an ongoing survival benefit with trastuzumab?[10] To what extent and for what duration will effects persist?
- Are the treatment benefits likely to occur in clinical practice where the patient group is likely to be more heterogeneous?
- How long should trastuzumab treatment be continued?
- Is the trastuzumab-induced cardiac toxicity reversible?
- Is sequential treatment with trastuzumab less cardiotoxic in the long-term compared with concurrent treatment?
- What is the risk-benefit of different treatment regimens (e.g. CT and concurrent transtuzumab appears to be more effective but more cardiotoxic)?
- What are the long-term cardiac outcomes?

Summary

In summary, under the analysis' base case scenario (the assumption of circumstances such as dosage, price, length of benefit etc. that PHARMAC staff consider to be most likely) the cost per QALY is estimated to be between $70,000 and $80,000 (12.5 to 14.3 QALY's gained per $1 million invested). While cost effectiveness is not the only criterion PHARMAC uses in its decision process, most treatments that PHARMAC has invested in have a cost per QALY of below $40,000 (25 QALY's gained per $1 million invested), with an average of $13,700 per QALY in 2004/05.

Sensitivity analysis was undertaken on the base-case scenario. The results of the CUA were very sensitive to the cost of trastuzumab, duration of treatment, the assumed length of benefit (i.e. reduction in risk for recurring breast cancer), and the discount rate used. This resulted in a very wide range of potential values for cost-effectiveness depending on assumptions and costs incorporated in the analysis.

Based on the available information it is not possible to determine with sufficient certainty whether or not trastuzumab is a cost-effective investment (relative to other pharmaceutical investment options) at this time. In order for trastuzumab to be considered as a cost effective investment either:

- the overall cost would have to reduce significantly through a reduction in treatment duration (with the same clinical benefit) or through a significant price reduction; or
- the clinical benefit continues to increase following discontinuation of treatment (i.e. the disease free survival curves continue to diverge). It will however be several years before this information is available.

[10] Note that the model assumed there is a long-term survival benefit associated with trastuzumab, as patients are less likely to relapse.

Appendix One

Minutes of the 16 February 2006 Pharmacology and Therapeutics Advisory Committee (PTAC) meeting relating to trastuzumab (Herceptin) in Her2+ early stage breast cancer - *(Item 20. Paragraph 20.19 as amended in May 2006)*

20. Trastuzumab (Herceptin)

20.1. The Committee considered an application from Roche relating to the use of trastuzumab (Herceptin) for early breast cancer. The Committee noted that trastuzumab has not been registered for use in early breast cancer, although Roche had submitted an application to Medsafe. Members further noted that trastuzumab had not yet been licensed for this indication in any other country. The Committee noted that it was unusual for PTAC to consider applications for unregistered medicines or for unregistered indications of registered medicines. However, PTAC noted the high level of public concern and considered that they could give a preliminary view.

20.2. The Committee noted that the application was for adjunctive treatment of HER2-positive early breast cancer for patients who have previously undergone surgery and a course of chemotherapy. Members noted that trastuzumab is currently registered and funded for the treatment of metastatic disease.

20.3. The Committee noted that patients with HER2-positive breast cancer (around 20%) have a poorer prognosis than for patients with other breast cancers, with an average survival of approximately 50% after ten years.

20.4. The Committee noted that the submission focused primarily on two studies published recently in the New England Journal of Medicine, the first by Piccart-Gebhart et al – reporting interim results of the HERA trial, and the second by Romond et al – reporting a pooled analysis of data from study B-31 and partial results of study N9831. The Committee noted that all studies were open label.

Piccart-Gebhart et al (HERA trial)

20.5. Members considered the paper by Piccart-Gebhart et al (N Engl J Med. 2005 Oct 20; 353(16): 1659-72.), an interim analysis after 1 year of a planned 2-year study. Members noted that this was an unblinded study.

20.6. The Committee noted that the HERA trial was divided into three treatment arms:

- Arm 1: trastuzumab for one year (1694 patients)
- Arm 2: trastuzumab for two years (1694 patients)
- Arm 3: observation (1693 patients)

20.7. Members noted that the HERA trial results were analysed early, and that the paper reported only the results from arm 1 and arm 3. The Committee considered that the interim results from the second arm should also have been available to the authors, but noted that they were not included in the analysis.

20.8. The Committee noted that the primary measure in the HERA trial was disease-free survival; secondary measures included cardiac safety, overall survival, site of first disease-free survival event and time to distant recurrence.

20.9. The Committee noted that for patients followed up to two years (16% of enrolled patients) there was an 8.4% absolute increase in disease-free survival in the trastuzumab arm although there was, as expected, no significant increase in overall

survival. Members further noted that 98% of patients enrolled in the study were alive at two years.

20.10. Members noted that there were fewer distant metastases in patients treated with trastuzumab, although there appeared to be an increased incidence of central nervous system metastases in patients treated with trastuzumab. Approximately one quarter of women in the trastuzumab arm who developed distant disease had central nervous system metastases.

20.11. The Committee noted that there was an increase in heart failure with trastuzumab and that at two years, 0.5% of patients in the treatment arm had developed moderate to severe (NYHA grade III or IV) heart failure (0% in placebo group). 7.1% experienced a decrease in left ventricular ejection fraction (LVEF) compared with 2.2% in the observation arm. Members noted that, in addition, 143 patients (8.5%) withdrew from the trastuzumab arm, most withdrawals appeared to follow adverse events. Members considered that it was not clear from the report whether these patients were included in the reported heart failure events.

20.12. The Committee noted that in the study, patients had their cardiac function assessed immediately following chemotherapy, and patients were excluded from commencing therapy with trastuzumab if their LVEF was less than 55%. Members noted that in New Zealand, patients could typically wait up to six months for an echocardiogram. This could mean that, if patients were to begin treatment with trastuzumab immediately following chemotherapy, they could possibly be doing so without having their cardiac function assessed. Members considered that this was an issue that would need to be addressed, should DHBs decide to fund trastuzumab for early breast cancer.

20.13. Members noted that they would like to review the 1-year data from the 2-year trastuzumab arm, and the longer-term data of the other arms when available.

Romond et al

20.14. Members considered the paper by Romond et al (N Engl J Med. 2005 Oct 20; 353(16): 1673-84.), pooled results of study B-31 and some of the results of N9831. Members noted that these studies were divided into the following treatment arms:

B-31
Arm 1: 12 weeks of paclitaxel
Arm 2: 12 weeks of paclitaxel plus trastuzumab for one year (started at same time)

N9831
Group A: 12 weeks of paclitaxel
Group B: 12 weeks of paclitaxel then trastuzumab for one year
Group C: 12 weeks of paclitaxel plus trastuzumab for one year (started at the same time)

20.15. The Committee noted that the results of each trial had not been published separately, and considered that, rather than a pooled analysis being published, each trial should have been published individually, with a subsequent meta-analysis (not a pooled analysis). Members noted that there were some significant differences between the papers that make comparison difficult, such as the timing of paclitaxel and the use of hormonal and radiation therapies. Members also noted that both trials were unblinded.

20.16. The Committee noted that the results of Group B of study N9831 were not included in the report, and that this was the only arm in the two studies that was of direct relevance to the application. Members considered that the efficacy results of this paper are of limited value.

20.17. The Committee noted that at median follow-up (2 years) there was a 9.6% absolute increase in disease-free survival in the trastuzumab arm, an 11.7% increase by three

years, and by 4 years of follow-up an 18.2% increase. Members noted, however, that the 4-year follow-up data were based on relatively few patients; 165 patients (5% of the 3351 enrolled in the studies) had data out to 4 years, with 133 alive at that time.

20.18. The Committee considered that while it was possible that disease-free survival could translate into overall survival in the long-term, there was insufficient evidence upon which to extrapolate this benefit reliably. However, the Committee noted that there were 62 deaths in the trastuzumab arm and 92 in the control arm of the report, with an overall survival increase of 2.5% at three years, and 4.8% at four years.

20.19. The Committee noted that adverse cardiac events for each trial were reported separately. In trial B-31 there was an increased rate of severe (NYHA III or IV) heart failure or death at 3 years, of 4.1% in the trastuzumab arm versus 0.8% in the observation arm. In trial N9831, the rate of severe (NYHA III or IV) heart failure or death was 2.9 % in the trastuzumab arm versus 0% in the observational arm. The Committee noted further that the pooled rate of discontinuation in this paper was even higher than in the HERA trial, with 364 (31.4%) patients having discontinued treatment with trastuzumab in the first year, 164 (14.2%) due to asymptomatic decreases in LVEF and 54 (4.7%) due to symptoms of cardiac failure or other adverse cardiac effect). Members also noted that patients taking trastuzumab appeared to have an increase in adverse respiratory side-effects, with four patients in trial B-31 developing interstitial pneumonitis, one of whom died.

General

20.20. The Committee considered that the long-term cardiac safety of trastuzumab is unclear, and that there is insufficient evidence to indicate whether the risks are dose-related, or if they are reversible upon cessation of treatment.

20.21. The Committee considered that both the benefit and safety data for trastuzumab in early breast cancer were premature at present.

20.22. The Committee noted that the increased risk of heart failure would also be present when used in metastatic disease, but that in this situation the risk/benefit ratio is considered to be acceptable. Members noted that with early disease around 50% of patients are still alive after 10 years, whereas with metastatic disease none would be alive at this time – therefore consideration of the long-term risk of severe heart failure is more important when treating early disease than in metastatic disease. The Committee considered that in the case of early disease, the addition of trastuzumab could put at risk patients who would otherwise have survived.

20.23. The Committee considered that if trastuzumab was to be used for early breast cancer, then that patient's cardiac status would need to be monitored throughout treatment, and that there would be resultant increases in non-pharmaceutical expenditure.

20.24. The Committee noted that discontinuation rates for those undergoing trastuzumab in the trials were reasonably high, and that this was despite strict exclusion criteria and high levels of monitoring.

20.25. The Committee noted that the projected $30 million cost per year was based on one year of treatment per patient, but noted that the trial data for two years would be available soon, and might indicate that there was a significant benefit in longer treatment. If this was the case the cost would be in the nature of $60 million per year.

20.26. One member noted that there may be other priorities for breast cancer control that may confer greater population health gains than by funding trastuzumab to the above extent. These might include improved access to services and earlier presentation, diagnosis and follow up in order to reduce the numbers of patients presenting with more advanced breast disease.

20.27. The Committee considered that it could not recommend listing at this time. Members considered that before making a recommendation, the Committee should wait until trastuzumab received approval from Medsafe for use in early disease.

20.28. The Committee **recommended** that in the meantime, to maintain progress with the application for funding, PHARMAC staff should request that Roche supply the individual results of the trials B-31 and N9831, a meta-analysis (not pooled) of those two trials, and details of complete follow-up of all patients in all three studies considered to date, including all-cause mortality.

20.29. The Committee **recommended** referring the application to CaTSoP once these have occurred. The CaTSoP recommendation will then be taken to PTAC for a final listing recommendation.

Appendix Two

Minutes of the 25 May 2006 Pharmacology and Therapeutics Advisory Committee (PTAC) meeting relating to trastuzumab (Herceptin) in Her2+ early stage breast cancer - *(Item 11)*

11. Trastuzumab (Herceptin)

11.1. The Committee noted that it had first reviewed the application from Roche Pharmaceuticals for the listing of trastuzumab (Herceptin) for early HER-2 positive breast cancer at its February 2006 meeting, prior to Medsafe registration. The Committee had requested that further information be provided in relation to any extended benefits and risks and that the Cancer Treatments Subcommittee of PTAC (CaTSoP) review the application.

11.2. The Committee noted that CaTSoP had reviewed the application on trastuzumab in April 2006. The Committee noted that: the supplier had provided a cost-utility analysis (CUA) on the use of trastuzumab in early HER-2 positive breast cancer; PHARMAC staff had undertaken a preliminary cost-utility analysis; and that further information had become available on the efficacy and alternative dosing schedules for trastuzumab since the previous meeting, including evidence provided by the supplier.

Minutes of CaTSoP

11.3. The Committee agreed with the considerations of the April 2006 meeting of CaTSoP regarding trastuzumab for early HER-2 positive breast cancer.

Further Clinical Information

11.4. The Committee considered that the evidence provided in the supplier's addendum to the Submission for trastuzumab did not meet the requirements of their request for information in February 2006.

11.5. Members noted that there was no further information supplied on Arm Two (trastuzumab treatment for two years) of the HERA trial (whose interim results for the one-year treatment and observation-only arms were published by Piccart-Gebhart et al N Engl J Med. 2005 Oct 20; 353(16): 1659-72). The Committee considered that these data should soon be available and consideration of these results would be important in any recommendation made.

11.6. Members noted that although the supplementary appendix to the Romond et al (N Engl J Med. 2005 Oct 20; 353(16): 1673-84) paper, as posted on the NEJM website, had been provided, the full individual results of the NSABP B-31 and NCCTG N9831 trials had not been provided as requested.

11.7. Members noted that the data contained in that appendix for the disease-free survival curves showed similar and statistically significant differences in favour of concurrent trastuzumab therapy, compared to no trastuzumab therapy, in each of the B-31 and N9831 trials. Members noted an early, unpublished analysis of disease-free survival in the N9831 trial supplied in the form of MS PowerPoint slides of a conference presentation (Perez et al. NCCTG N9831: May 2005 update, presentation at the 41st American Society of Clinical Oncology conference, May 2005). Members noted that sequential trastuzumab treatment (Arm B) was not statistically superior to non-trastuzumab treatment (Arm A), but that concurrent trastuzumab treatment (Arm C) resulted in a significant improvement in disease-free survival compared with Arm B. Members considered that although these data were preliminary, they raised concerns about the optimal dosing schedule of trastuzumab treatment. Members noted that

slides from an oral presentation do not provide sufficient information to make necessary decisions.

11.8. The Committee noted results for the Breast Cancer International Research Group (BCIRG) 006 study (as yet unpublished) supplied in the form of MS PowerPoint slides of a conference presentation (Slamon D., SABCS 2005). It noted that there were three treatment arms: the first containing chemotherapy only, with four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel; the second containing the same chemotherapy regimen plus one year of trastuzumab commenced concurrently with docetaxel; and the third comprising six cycles of docetaxel and carboplatin with one year of trastuzumab commenced concurrently with the chemotherapy. Members noted that there was a significant improvement in disease-free survival in the trastuzumab treated patients; however, there was no significant difference in disease-free survival between the two trastuzumab arms. There were insufficient data to evaluate overall survival.

11.9. The Committee noted the concerns raised by CaTSoP in its consideration of cardiac toxicity associated with trastuzumab. The Committee noted that a pooled data analysis provided by the supplier, including data from HERA, NSABP B-31, NCCTG N9831 and BCIRG 006 trials, indicated that cardiac effects appear to be manageable; however, the long-term impact of these cardiac effects is unknown.

11.10. The Committee noted that the rates of cardiac dysfunction appear to be lower when trastuzumab is administered sequentially, rather than concurrently, with chemotherapy. The Committee considered that trastuzumab treatment was associated with higher rates of cardiac toxicity when used with an anthracycline-containing chemotherapy regimen.

11.11. The Committee noted the results of a sub-analysis of patients with HER-2 positive breast cancer published as part of the FinHer Study (N Engl J Med. 2006 Feb 23; 354(8): 809-20). The Committee noted that this study had not been provided by the supplier.

11.12. The Committee noted that in the FinHer trial, patients were randomized to receive three cycles of either docetaxel or vinorelbine followed by three cycles of fluorouracil, epirubicin and cyclophosphamide. Patients with HER-2 positive breast cancer were further randomised to receive or not receive nine weekly infusions of trastuzumab commenced concurrently with the first cycle of chemotherapy. The Committee noted that, after a median follow-up of 36 months, trastuzumab treatment resulted in a significant improvement in disease-free survival compared with the control group (HR 0.42, p=0.01) without the cardiac toxicity associated with 12 months trastuzumab treatment as reported in other trials.

11.13. The Committee noted that the trastuzumab treatment arms of the FinHer trial were relatively small (232 of 1,010 patients) and that the trial might not have been sensitive enough to reliably detect cardiac toxicity. However, the Committee considered that, given the proposed molecular mechanisms of trastuzumab and anthracycline cardiotoxicity, the treatment sequence used in the FinHer study (i.e. trastuzumab prior to anthracycline) might have substantially reduced the risk of developing cardiac toxicity.

11.14. The Committee considered that the FinHer Study cast significant doubt over the optimal duration and timing of trastuzumab treatment. Members noted that funding trastuzumab for the proposed indication would have a high budgetary impact, which would have significant consequences for future funding of other pharmaceuticals and services. The uncertainty surrounding the optimal duration and timing of treatment represented a large risk that should be addressed before any decision is made.

General considerations

11.15. The Committee considered that it was highly unlikely that the strict entry and exit criteria in clinical trials of trastuzumab would be adhered to in clinical practice. It considered that there might be a higher rate of adverse effects associated with trastuzumab when used in clinical practice due to the likely difficulties in accessing the required cardiac monitoring services.

11.16. The Committee considered that the true benefit of trastuzumab in primary breast cancer in relation to its costs lay in the rate of overall survival compared with the duration of treatment. The Committee noted that, at this time, these data are immature.

11.17. The Committee considered whether trastuzumab would be used to treat a patient with metastatic breast cancer, if it had already been administered to that patient in the early stages of their breast cancer. The Committee considered that it might be difficult to enforce a restriction on the use of trastuzumab to either primary or metastatic breast cancer. It considered that some physicians would wish to use trastuzumab in both stages of disease if there was a significant time between treatments. The Committee considered that re-treatment with trastuzumab would significantly increase expenditure and was not supported by trial data. The Committee noted that CaTSoP considered that patients should not be re-treated with trastuzumab should the disease recur following treatment for the primary disease.

11.18. The Committee reiterated the minute of CaTSoP who considered that, at present, both infusion and echocardiogram services are working at, or near, capacity in DHB hospitals. If trastuzumab were available for early breast cancer, the Committee considered that it may result in increased waiting times for existing cancer treatments and adversely impact on cardiology services.

Cost-Utility Analysis

11.19. The Committee reviewed the cost-utility analyses on the use of trastuzumab in the primary setting. The Committee considered that length of relative benefit from trastuzumab would need to be addressed before any further work on other factors such as management of adverse effects was undertaken, to enable an estimate regarding the cost-utility of trastuzumab to be made reliably. The Committee considered that the availability of longer-term data would inform this process.

Recommendation

11.20. The Committee concluded that, based on the interim trial results published to date, trastuzumab may have a role in the treatment of primary breast cancer. However, the Committee considered that, with the data provided, they were unable to determine the optimum schedule and duration of trastuzumab treatment, the magnitude of treatment benefit on Overall Survival and, therefore, the cost-effectiveness of trastuzumab.

11.21. Given the high cost of trastuzumab, the early nature of the clinical data, and the significant impact on other services and investments in healthcare, which may offer better health outcomes for the money invested, the Committee did not consider it appropriate to make a recommendation for funding this product at this time. It noted that although there was insufficient evidence to make a positive recommendation at this time, it was likely that further data would enable the Committee to address it's questions regarding the long-term health benefits, optimal scheduling and cost-effectiveness of trastuzumab.

11.22. The Committee noted that it would welcome any substantial body of evidence from the supplier for consideration at subsequent meetings.

References

1. Piccart-Gebhart, M.J. Procter, M., Leyland-Jones, B. et al., Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. The New England Journal of Medicine 2005; 353(16): 1659-1672. http://content.nejm.org/cgi/content/full/353/16/1659

2. Romond, E.H., Perez, E.A., Bryant, J. et al., Trastuzumab plus Adjuvant Chemotherapy for Operable HER-2 positive breast cancer. The New England Journal of Medicine 2005; 353(16): 1659-1672. http://content.nejm.org/cgi/content/full/353/16/1673

3. Fourth adjuvant trial backs up Herceptin us. Scrip 2005; 3091:27

4. Genentech, Inc. (DNA) Release: Fourth phase III study shows Herceptin plus chemotherapy improved disease-free survival in early HER2-positive breast cancer, 13 September 2005.

5. Burnstein, H.J. The distinctive nature of HER-2 positive breast cancers. New England Journal of Medicine 2005; 353(16); 1652-1654.

6. Piccart-Gebhart M.J., Procter, M., Leyland-Jones, B., et al., Trastuzumab (Herceptin) and HER2-positive breast cancer. Canadian Medical Association Journal. 2006; 174 (1): 36-37

7. Hudzial, R.M., Schlessinger, J., Ullrich, A. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 313 cells. Proceedings of the National Academy of Science USA 1987; 84; 7159-7163.

8. Smith, I. and Chua, S. Medical treatment of early breast cancer 3: chemotherapy. British Medical Journal 2006;332:161-162

9. Sun, J.M., et al., Clinical relevance of HER-2 expression in node-negative breast cancer patients. *Journal of Clinical Oncology*, ASCO Annual Meeting Proceedings (Post-Meeting Edition) 2004; (22)14S (July 15 Supplement): 598

10. Herceptin data sheet. Trastuzumab 150mg and 440mg powder for concentrate for solution for infusion. Roche datasheet, 10th October 2005.

11. PHARMAC Pharmaceutical Schedule, 2005 (December): 136

12. Medsafe Datasheet, http://www.medsafe.govt.nz/profs/Datasheet/h/Herceptininf.htm (accessed 11th January, 2006)

13. Ewer, M.S., Vooletich, M.T., Durand, J.B., et al., Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. Journal of Clinical Oncology. 2005:23(31);7820-7824.

14. Vogel, C.L., Cobleigh, M.A., Tripathy, D., et al., Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2- overexpressing metastatic breast cancer. Journal of Clinical Oncology. 2002: 20(3); 719-726.

15. 15. National Comprehensive Cancer Network. Practice oncology Guidelines – Invasive Breast Cancer. Available at : http://www.nccn.com/professionals/physician_gls/PDF/breast.pdf accessed January 2006.

16. National Institute For Health And Clinical Excellence. Final Appraisal Determination. Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer, June 2006. http://www.nice.org.uk/page.aspx?o=328476.

17. London Cancer New Drugs Group - Interim recommendations for trastuzumab (Herceptin) in early breast cancer. Available at http://www.druginfozone.nhs.uk/Record%20Viewing/viewRecord.aspx?id=557310 (accessed January 2006)

18. Bramley D, Lund M, Tracey J, Echocardiography, congestive heart failure and integrated care. NZFP. 2002: 29; 313-317

19. Neave L, Harvey V, Benjamin C, Thompson P, Pellett O, Whitlock J, Jones W, Poole G; Auckland Breast Cancer Register Auckland Breast Cancer Study Group. The Auckland Breast Cancer Register: a special project of the Auckland Breast Cancer Study Group. N Z Med J. 2003 Oct 24;116(1184):U648.

20. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 May 14-20;365(9472):1687-717.

21. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001 Mar 15;344(11):783-92.

22. Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol. 2002 Sep 1;20(17):3628-36.

23. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1-12.

24. Devlin N, Hansen P, Kind P, Williams A. The health state preferences and logical inconsistencies of New Zealanders: a tale of two tariffs. CHE Discussion paper 180, University of York, 2000.

25. Mathers C, Vos T, Stevenson C 1999. The burden of disease and injury in Australia. AIHW cat. no. PHE 17. Canberra: AIHW. http://www.aihw.gov.au/publications/index.cfm/title/5180

26. Murray CJL, Lopez AD (eds). The global burden of disease: a comprehensive assessment of mortality and disability from disease, injuries, and risk factors in 1990 and projected to 2020. Harvard School of Public Health on behalf of the World Health Organisation and the World Bank. Boston: Harvard University Press, 1996.

27. Stouthard MEA, Essink-Bot M, Bonsel GJ, Barendregt PGN, et al. Disability weights for diseases in the Netherlands. Rotterdam: Department of Public Health, Erasmus University, 1997.

28. National Horizon Scanning Centre. Trastuzumab as adjuvant therapy for early stage breast cancer - horizon scanning review. Birmingham: National Horizon Scanning Centre (NHSC), 2005. http://www.pcpoh.bham.ac.uk/publichealth/horizon/

29. Scottish Intercollegiate Guidelines Network (SIGN). Grading System for Recommendations in Evidence-Based Clinical Guidelines. Report of a review of the system for grading recommendations in SIGN guidelines, March 2000.

http://www.show.scot.nhs.uk/sign/,
http://www.nzgg.org.nz/tools/Grading%20System%20for%20Recommendations%20-%20Review%20Report.pdf

30. Neyt M, Albrecht J, Cocquyt V. An economic evaluation of Herceptin in adjuvant setting: the Breast Cancer International Research Group 006 trial. Ann Oncol. 2006 Mar;17(3):381-90. Epub 2005 Nov 30. http://annonc.oxfordjournals.org/cgi/content/full/17/3/381

31. National Institute for Clinical Excellence, 2002. http://www.nice.org.uk/page.aspx?o=29280

32. Elkin et al. HER-2 Testing and Trastuzumab Therapy for Metastatic Breast Cancer: A Cost-Effectiveness Analysis. Journal of Clinical Oncology, Vol 22, No 5 (March 1), 2004: pp. 854-863. http://www.jco.org/cgi/content/full/22/5/854.

33. Pritchard KI, Shepherd LE, O'Malley FP, Andrulis IL, Tu D, Bramwell VH, Levine MN; National Cancer Institute of Canada Clinical Trials Group. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med. 2006 May 18;354(20):2103-11. http://content.nejm.org/cgi/content/full/354/20/2103. from Figure 1. Relapse-free Survival (Panel A) and Overall Survival (Panel B) among Women with Breast Cancer, According to HER2 Amplification Status on FISH.

34. FinProg data (http://www.finprog.org/) – HER2-positive vs. HER-2 negative

35. PHARMAC analysis of Cancer Register registration data for female breast cancers 1991 to 2005, supplied by NZHIS.

36. 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 Feb 23;354(8):809-20. http://content.nejm.org/cgi/content/full/354/8/809

37. Ward S, Pilgrim H, Hind D. Trastuzumab for the Treatment of Primary Breast Cancer in HER2 Positive Women: A Single Technology Appraisal. University of Sheffield School of Health and Related Research (ScHARR), May 2006. http://www.nice.org.uk/page.aspx?o=328487. Update with revised cost per QALY at at http://www.nice.org.uk/page.aspx?o=328530.

38. Rosevear M. PHARMAC and Herceptin for early-stage breast cancer in New Zealand: Herceptin or deception? N Z Med J. 2006 Jun 2;119(1235):U2014. http://www.nzma.org.nz/journal/119-1235/2014/

39. Petersen S, Rosevear M. Roche responds to the 'Herceptin or deception' article—and response by the article's author. N Z Med J. 2006 Jul 7;119(1237):U2069. http://www.nzma.org.nz/journal/119-1237/2069/

PART 2

Supplementary Technology Assessment Report No. 75b

9 week concurrent trastuzumab (Herceptin) treatment in HER-2 positive early breast cancer

(supplement to TAR 75 of August 2006)

Type: Preliminary Cost-Utility Analysis
Last Updated: March 2007

Appendix One details the more recent relevant PTAC minutes from August and November 2006 and February 2007.

Appendix Two provides a qualitative update of the original CUA (Part 1, TAR 75) for the HERA 23-month median follow-up results.

Appendix Three summarises the relevant clinical trials.

Appendix Four compares and contrasts the 12-month sequential and 9 week concurrent regimes in terms of patient numbers, costs and cost-effectiveness.

Appendix Five and Six: details further clinical evidence information

Rapid Cost-Utility Analysis (CUA) for 9 weeks trastuzumab regimen

Background

The cost-utility analysis for twelve months sequential trastuzumab treatment regimen was based on the 12 months median follow-up data from the HERA trial (Piccart-Gebhart *et al.,* 2005), and is described in Part 1 TAR 75 'Trastuzumab (Herceptin) in HER-2 positive primary breast cancer' (last updated August 2006). This cost-utility analysis was revised to estimate the incremental cost and benefit of treating HER-2 positive early breast cancer with a nine week concurrent course of trastuzumab (as per the FinHer regimen (Joensuu *et al*, 2006)).

Initial cost-utility analysis of the nine week regimen identified that, under reasonable assumptions (and with efficacy rates similar or better than those of the 12 months model), nine weeks concurrent treatment would be cost-effective relative to other funding options. Therefore, the entire analysis, but in particular the sensitivity analysis that is presented in this supplementary Part 2 TAR (75b), is more focussed on verifying whether the nine week regimen would remain cost-effective under conservative, pessimistic assumptions. Generally, those assumptions or inputs that were shown to improve the cost-effectiveness of trastuzumab in the sensitivity analysis for the original model were not analysed or updated in the current model (see Part 1, TAR 75).

As has been previously described, the FinHer trial is small in comparison with HERA, which gives us less confidence in the results. 231 patients in FinHer were HER2 positive and were randomised to receive either trastuzumab or no trastuzumab, on top of their docetaxel or vinorelbine (total 1,010 patients). However, FinHer did report a statistically significant result for disease free survival (DFS) which is comparable with the results seen in HERA. Those patients who received trastuzumab had better three-year DFS than those who did not receive trastuzumab (12/115 vs. 27/116, 89% compared with 78%, hazard ratio (HR) = 0.42 (95% CI 0.21-0.83)) (Joensuu *et al*, 2006).

PTAC and CaTSoP reviewed the FinHer trial in 2006, and recommended that the nine week concurrent trastuzumab treatment regimen be given a high priority recommendation for funding. The relevant minutes of these Committee meetings are included as Appendix One[11] of this document.

Further details on FinHer, including discussion about its patient numbers and information regarding patient overall survival, can be found in Appendices Five and Six of this Part 2 Supplementary TAR 75b. Given that the efficacy of FinHer is discussed elsewhere, this issue is not addressed further within this TAR, except for the analysis showing the effects of reduced assumptions on the efficacy.

Updated Clinical Information

The majority of clinical information for this analysis is described previously in the main analysis (Part 1 TAR 75 'Trastuzumab (Herceptin) in HER-2 positive breast cancer', last updated August 2006). Only deviations from these original inputs are described in this preliminary CUA update.

The cost-utility analysis for 12 months sequential trastuzumab treatment has not been updated to include, amongst other changes in information, the new evidence (23 months follow-up data for HERA published in the Lancet in January 2007 (Smith *et al.,* 2007),

[11] Appendix One to this report contains the relevant subsequent CaTSoP and PTAC minutes since mid 2006 (ie those not included in Part 1 TAR 75 'Trastuzumab (Herceptin) in HER-2 positive breast cancer', last updated August 2006). The minutes included are those from relevant PTAC meetings in August and November 2006 and February 2007, and also the October minute from the Cancer Treatments Subcommittee of PTAC (CaTSoP).

and the related editorial (Hind *et al.,* 2007)). PHARMAC staff believe that inclusion of all the new information would only serve to make the 12 month sequential regimen less cost-effective (than the current base case result of $70,000-$80,000/QALY). For further details, see Appendix Two for a rapid qualitative update of the original CUA (Part 1, TAR 75).

Appendix Three summarises the relevant clinical trials. Appendix Four compares and contrasts the twelve months sequential and nine week concurrent regimens in terms of patient numbers, costs and cost-effectiveness. Appendix Five and Six detail the rationale and clinical evidence underlying the nine week concurrent treatment regimen.

Clinical Inputs for CUA:

Reduced risk of cancer recurrence:

The relative risk of recurrence (i.e. benefit of treatment) for the revised nine week analysis is taken from the twelve months median follow-up interim results for disease progression in the HERA trial (as in the model for the original CUA for twelve months sequential treatment). The transition probabilities in FinHer were, in fact, better than those for HERA (i.e. the recurrence of disease was lower – the hazard ratio (HR) in FinHer was 0.42, compared with HERA's HRs of 0.54 and 0.64 for the interim twelve-month and the updated 23-month median follow-up results respectively – see Appendix Two). Therefore, using the HERA transition probabilities may be a conservative estimate of treatment benefit, and therefore may understate cost-effectiveness of the nine week concurrent regimen.

These transitional probabilities relating to efficacy are varied in the sensitivity analysis (described below).

Numbers of patients treated:

Patients with sufficient heart function: The FinHer regimen administers trastuzumab prior to cardiotoxic chemotherapy (anthracyclines). The original twelve months budget impact analysis and CUA did not correct patient numbers for anthracycline induced heart dysfunction prior to trastuzumab administration. Therefore, the original analysis overestimated the number of patients who would be eligible for twelve months sequential trastuzumab by 15-20%.

PHARMAC staff estimate that 15-20% more patients could receive trastuzumab treatment under the nine-week regimen because patients will not have yet received cardiotoxic chemotherapy. However, since the original analysis did not adjust for this reduction in eligible patients, this updated analysis did not make amendments to the eligible patient pool in this respect.

The original analysis used age-adjusted cardiac risk to determine the number of HER-2 positive patients who would meet the criteria for trastuzumab. The updated analysis uses information on LVEF function for women in this age group. As a consequence, more patients would be expected to receive trastuzumab under these new assumptions. Note however, that this amendment to the inputs to the model for twelve months sequential treatment would not change its cost-utility analysis result, only the budget impact analysis result.

Prevalence of HER-2 positive disease: The frequency of HER2 positive early breast cancer was assumed to be 17%. As described previously (Description of disease, page 4 of the original TAR 75), there is conflicting evidence as to the proportion of patients with early breast cancer who have HER2 positive disease. This 17% is an updated estimate for prevalence of HER2 overexpression in early disease (the original TAR used a prevalence of 24% for HER2 positive disease). This lower percentage of HER-2 positive patients confers in a higher cost of testing for each treated patient (more patients will test negative for HER2 status and not receive treatment with trastuzumab). As such this change to the CUA inputs is a conservative assumption (ie. disfavours trastuzumab).

Disease progression:
As discussed previously (page 34 of original TAR 75), the original twelve months sequential trastuzumab CUA model models a steep disease progression curve for HER2 cancer. This implies a higher baseline mortality than would be expected in the placebo arm. As a result, the original CUA model favours trastuzumab. In the revised nine week model the baseline risk for disease progression has been lowered by 10% in order to closer align the modelled mortality with observed data for HER2 positive disease progression. The effect of different disease progression rates has been tested in the sensitivity analyses.

Cardiac toxicity and adverse event rates:

The rates of cardiac toxicity were assumed to occur at the same rate as described in the original model (which is based on a 6 month cycle, where patients receive two cycles of treatment in the original model, equating to twelve months trastuzumab treatment). Therefore, patients can experience an adverse event only in the first 6 months of this model, effectively meaning that the incidence of adverse events is reduced by half.

The FinHer trial did not report an increased incidence of cardiac events (in fact there were no cardiac events recorded in the trastuzumab arm) in patients treated with trastuzumab compared with those in the control arm. The adverse events reported in the FinHer paper are limited to neutropenia, which appeared to be rectified by a docetaxel dose reduction in the protocol. The FinHer paper states that trastuzumab did not significantly increase the frequency of adverse effects related to either docetaxel or vinorelbine.

However, because FinHer's small sample size may mean that the study is underpowered to detect and measure cardiotoxicity or other adverse effects, the revised nine week model retains the increased rates of cardiotoxicity as described in the HERA trial and used in the original model.[12] Because there is some scientific evidence to suggest that pre-anthracycline treatment with trastuzumab could be less cardiotoxic than post-anthracycline administration, the current model may overestimate the rate of adverse effects that would occur in clinical practise (and therefore may underestimate the benefits and overestimate the costs of this regimen in clinical practise).

Costs of nine week concurrent regimen:

The nine week treatment regimen would incur costs over the current costs of standard care HER-2 positive early breast cancer treatment regimen. It is assumed that patients would undergo the same treatment regimen as patients in the FinHer trial – i.e. a nine week course of trastuzumab administered concurrently with a taxane (in this case, docetaxel, see below) (Joensuu *et al*, 2006).

Costs of testing: [redacted] All patients will have immunohistochemistry (IHC) tests to diagnose if the tumour is over-expressing the HER2 gene. The cost of an IHC test is $160 per patient. The cost for the FISH test is $350, with 20% of all early breast cancer patients assumed to require this test to confirm HER2 status. In effect, since the entire population needs to be tested to determine which patients require trastuzumab treatment,

[12] The low cardiotoxicity observed in FinHer could also be explained by the relatively low cumulative dose of anthracycline chemotherapy (180 mg/m^2 epirubicin while the maximum tolerated cumulative dose of epirubicin is of 720mg/m^2). In the B31/N9831 studies doxorubicin was administered at a cumulative dose of 240 mg/m^2 (Romond *et al.,* 2005) while its maximum tolerated cumulative dose is 500 mg/m^2. Epirubicin is generally presented as a less cardiotoxic agent than doxorubucin. Indeed, as stated in the FinHer paper, the small size and the short duration of the follow-up are limitations of the study and the optimal duration of adjuvant trastuzumab therapy is not known and may be clarified only in further randomized trials (KCE 2006).

the total cost per treated patient needs to be multiplied by 1/proportion of HER2 positive patients.

Patients who are to receive trastuzumab must have adequate heart function. Therefore, all patients who test HER-2 positive are assumed to incur the cost of an initial visit to the cardiologist and an Electrocardiogram (ECG). The table below shows the costs incurred by testing these patients.

Table 1: Costs of testing for HER-2 over-expression

Item	Cost
Number of early breast cancer patients per year	2270-2660
Total (IHC) cost per patient	$160
Total FISH cost per patient	$80
Frequency (HER2 positive patients)	17%
Initial Cardiac Function assessments (HER2 positive patients only)	$250

Cost of cardiac monitoring: For the nine week analysis it was assumed that patients would have one further ECG whilst taking trastuzumab and 50% of patients (at most) would have an echocardiogram at the cost of $340.

Pharmaceutical costs:

Cost of trastuzumab: [redacted] the per mg cost of trastuzumab used in this model is $8.81 per mg as listed on the Pharmaceutical Schedule. The model also includes a [redacted] increase on drug cost as an estimate for the costs of compounding and wastage. Patients are assumed to receive 20mg/kg total dose of trastuzumab (as per the FinHer regimen ((Joensuu *et al*, 2006)).

Assuming an average weight of 70.9kg (with a normal distribution to account for a normal weight range in this patient population), this translates to a mean total dose of 1440mg per patient.

Cost of taxane treatment: In addition to the cost of trastuzumab and its administration, there is also an incremental cost for the nine week concurrent regimen due to concomitant administration of docetaxel (Taxotere) with trastuzumab which is not currently funded for early breast cancer. Paclitaxel is currently the only funded taxane for breast cancer in New Zealand, and a generic is available.

Paclitaxel is currently indicated for node positive patients as standard care chemotherapy. Under this nine week model all patients (node positive and node negative) receiving trastuzumab are assumed to receive concurrent docetaxel.

Docetaxel is significantly more expensive than paclitaxel, and the total incremental cost per patient (trastuzumab and docetaxel) is shown in the table below. However, a generic version of docetaxel is expected to become available in the near future. The cost-effectiveness of this treatment regimen with the generic cost of docetaxel favours trastuzumab and is considered in the sensitivity analysis.

Cost of epirubicin: Status quo treatment for early breast cancer is assumed to be combination treatment with 5-Flurouracil (5-FU), doxorubicin and cyclophosphamide (FAC). Node positive patients receive 4 cycles of FAC followed by taxane

chemotherapy (paclitaxel, as described above). It is assumed that node negative patients receive 6 cycles of FAC under status quo treatment.

The incremental cost for epirubicin compared with doxorubicin is small (~$100 per patient on average), therefore the substitution of epirubicin for doxorubicin is not factored into this analysis.

Cost of administration (over and above the cost of standard care). Three extra infusions (an average) were included in the analysis to factor in the extra costs and resources for DHBs associated with administering trastuzumab.

Note that for node positive patients (who would receive taxane treatment in standard care) this is likely to overestimate the number of extra infusions required.[13]

This CUA models the worst case incremental cost scenario – that all patients incur drug costs for both trastuzumab and docetaxel, and patients will receive an additional three infusions over and above standard chemotherapy as part of the nine week trastuzumab treatment regimen. However, the additional cost of substituting epirubucin for doxorubicin is not included.

The total incremental cost to DHBs per patient is described in the following table.

Table 2: Estimated incremental cost to DHBs per patient

Item	Cost (year 1 prices)
Total drug cost per patient (weighted average)[1,2]	**$17,200**
DHB Service Costs	
Infusions Costs	$350
Cardiac monitoring[3]	$232
Total cost of services per patient	$300
Total Cost per patient (weighted average)[2]	$17,500

1 Assumes averaged weight patient of 70.9 Kg, BSA 1.7m^2

2. Assumes that patients will be administered nine weeks trastuzumab concurrent with docetaxel rather then paclitaxel.

3. Assumes all patients receive 1 ECG prior to trastuzumab treatment, 1 ECG whilst on trastuzumab treatment, and 50% of patients will require an echocardiogram.

Cost of disease progression

The costs of disease progression are documented previously for the original twelve months model (TAR 75 page 24). It should be noted however that the cost of distant relapse currently includes the cost of another course of trastuzumab, and if this was removed (i.e. funding criteria would only allow patients to receive one course of trastuzumab), this would improve the cost-effectiveness of trastuzumab.

Results: cost-effectiveness of the nine week concurrent regimen

The analysis of the nine weeks concurrent regimen resulted in a base case (with assumptions that generally favour standard treatment, i.e. a slightly pessimistic view of 60 QALYs per million to 65 QALYs per million net costs to Vote:Health, (i.e. $14,500-$16,500/QALY) at current prices for trastuzumab and docetaxel. This could improve to over 90 QALYs per million ($11,000/QALY) once docetaxel becomes generic (resulting in a price reduction).

Assuming that nine weeks treatment is efficacious (see Appendices One, Five and Six for a discussion of this assumption in detail), it is considered cost-effective when compared with other pharmaceutical treatment options that PHARMAC has funded, or is considering funding.

Sensitivity Analysis

The twelve months model was tested extensively under one way sensitivity analyses, to determine the extent to which changes in the inputs would change the cost-effectiveness ratio (i.e. make it more or less cost-effective). As this is a preliminary analysis, most of the sensitivity analysis scenarios concentrated on testing the variables that the model was already known to be sensitive to (see Original analysis in Part 1, TAR 75).

The limitations of the FinHer trial, (ie as a result of the small numbers of patients) mean that there may be concerns regarding the validity of the results (see Appendices One, Five and Six for a description of these limitations). Therefore, sensitivity analysis was conducted on this model to determine the effect of reduced efficacy on the cost-effectiveness result. The FinHer trial results for disease free survival were HR 0.42 (95% CI 0.21-0.83). Sensitivity analysis examined the cost-effectiveness of a scenario where the effectiveness of trastuzumab was reduced to the level of the upper confidence interval limit (i.e. HR 0.83, or a 17% reduction in risk of recurrence of disease) as the 'worst-case' scenario for effectiveness of the nine weeks regimen[14].

[14] Note that the use of 17% risk reduction for disease recurrence in sensitivity analysis (derived from upper confidence interval limit of 0.83 in FinHer) is arguably an extremely pessimistic assumption. In comparison, the upper confidence limit for 12-month sequential treatment is as high as 0.81 (combining the HERA updated 23-month data with Arm B of NCCTG N9831, HR 0.70 (0.61-0.81), Perez, 2005)). Further details and references are described in Appendix Six.

The following table provides results for the one way sensitivity analyses:

Table 3: Sensitivity analysis results for nine week concurrent regimen

Variable	Base-Case Analysis	Sensitivity Analysis	QALY's gained per $ million	Cost per QALY
Base Case				**$15,900**
Risk of Relapse in both treatment arms.[15]	90% of risk in 12 month model	30% reduction	37	$27,200
Low efficacy (risk reduction)	46% (HERA 12-month interim DFS HR 0.54)	17% (FinHer HR upper CL 0.83)	17.5	$57,000
Additional cost of docetaxel (under generic scenario)	Cost of substituting docetaxel for paclitaxel	-40%	95	$10,500
Discount rate	8.0%	3.5%	145	$6,900
Discount rate	8.0%	0.0%	345	$2,900
Cost of palliative care	as per 12 month model	25% decrease	57	$17,500
Cost of trastuzumab	as per 12 month model	-15%	74	$13,500

Probabilistic sensitivity analysis could not be undertaken in the timeframe available with the current model structure, because it contains Monte Carlo tracker variables. However, this model is driven by a number of structural assumptions, including the assumed length of treatment benefit, the rate of disease progression, and the discount rate, all of which cannot be tested under probabilistic sensitivity analysis.

Using the above extreme assumption of reduced efficacy (17% reduction in risk of recurrence when treated with nine weeks trastuzumab, derived from the upper confidence limit for FinHer's hazard ratio for in disease recurrence), the nine weeks concurrent regimen has a cost per QALY of $57,000.

While there is still a large range of plausible outcomes within the CUA analysis, all are within what is generally considered to be cost-effective when compared to other options available for funding at this time. Even in the extreme worse case scenario sensitivity analysis (17% efficacy) the result stays above 17 QALY per million dollars spent ($57,000/QALY), which is still better than the base case result of the twelve months analysis, despite a far more conservative approach to the modeling the nine week analysis compared with the twelve months regimen.

In all other scenarios the results are well above 33 QALY per million dollars spent (below $30,000/QALY).

[15] Note that risk of relapse has already been reduced by 10% compared to the 12 month analysis, in order to modify the overstated disease progression modeled in the original analysis. Refer to 'Reduced risk of cancer recurrence'**:** page 52.

Conclusions and discussion of trastuzumab nine week concurrent regimen CUA results:

The nine week concurrent trastuzumab treatment regimen was given a high priority recommendation for funding by PTAC and CaTSoP (the independent clinical advisory committees to PHARMAC) in 2006. PHARMAC staff have updated the CUA for the incremental cost-effectiveness of adding a nine week concurrent course of trastuzumab to standard chemotherapy care, based on the treatment regimen used in the FinHer trial.

The CUA for the twelve month sequential regimen concluded that, given the uncertainty around the clinical data with regard to the length of treatment benefit, the base case for the twelve months sequential treatment regimen as described by HERA would result in 12.5 QALY per million dollars spent to 14.2 QALY per million net dollars spent by DHBs ($70,000-$80,000 per QALY), with an unusually wide range of outcomes that did not give enough certainty to determine whether twelve months of sequential trastuzumab was cost-effective.

Compared with current standard care (FAC chemotherapy), the nine week trastuzumab concurrent regimen is cost-effective when compared to other investment options for pharmaceuticals. While there is still uncertainty surrounding the extent of the benefits of treatment with trastuzumab, this is offset by the reduced costs and the improved cost-effectiveness of the nine week concurrent regimen. The likely range of cost-effectiveness results obtained from sensitivity analyses would still be considered to be cost-effective when compared to other funding options. An exception is the assumption of efficacy of trastuzumab being at the upper limit of the confidence interval from the FinHer study (17% relative reduction in disease events).

It should be noted that, assuming the efficacy of a nine week concurrent regimen is similar to that of the twelve months sequential regimen, then the nine week concurrent regimen is dominant (similar efficacy, lower cost) when compared with the twelve months sequential regimen. Indeed, even when using the upper limit of the confidence interval for efficacy (HR 0.83 – i.e. a 17% reduction in risk of recurrence) the nine week concurrent regimen remains more cost-effective than the base case result for the twelve months regimen ($57,000 vs $70-80,000). Therefore, no further direct comparison between twelve months sequential and the nine weeks concurrent treatment regimens has been performed (both analyses used standard care (FAC chemotherapy) as the comparator arm).

References for the nine week CUA (TAR 75b):

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 Feb 23;354(8):809-20. http://content.nejm.org/cgi/content/full/354/8/809

Romond, E.H., Perez, E.A., Bryant, J. et al., Trastuzumab plus Adjuvant Chemotherapy for Operable HER-2 positive breast cancer. The New England Journal of Medicine 2005; 353(16): 1659-1672. http://content.nejm.org/cgi/content/full/353/16/1673

Piccart-Gebhart, M.J. Procter, M., Leyland-Jones, B. et al., Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. The New England Journal of Medicine 2005; 353(16): 1659-1672. http://content.nejm.org/cgi/content/full/353/16/1659

Hind D, Pilgrim H, Ward S. Questions about adjuvant trastuzumab still remain. Lancet 2007; 369:3-5.

Belgian Health Care Knowledge Centre (KCE). Trastuzumab in early stage breast cancer. KCE reports vol. 34C, 2006. http://kce.fgov.be/index_en.aspx?ID=0&SGREF=5211&CREF=7198

Perez EA. Further Analysis of NCCTG-N9831. Slide presentation ASCO annual meeting 2005, available online at http://www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005815-00_21-001,00.asp

Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A. *et al.* 2 year follow up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007;369:29-36.

Appendix One:
Relevant Minutes of the clinical advisory committees since mid-2006

Error! Not a valid link.

Appendix Two:
Rapid update of TAR 75 for HERA 23 month follow-up information
Error! Not a valid link.

Appendix Three:
Trastuzumab Clinical trial summaries

Error! Not a valid link.

Appendix Four:
Comparisons between 12 month sequential and 9 week concurrent regimens
Error! Not a valid link.

Appendix Five:
Clinical information for trastuzumab - summary, interpretation and policy implications
Error! Not a valid link.

Appendix Six:

Clinical data

Error! Not a valid link.