PART 3

Further Supplementary Technology Assessment Report No. 75c

12 month trastuzumab (Herceptin) treatment in HER-2 positive early breast cancer, compared with 9 week concurrent treatment

(supplement to TAR 75 of August 2006 and its supplementary TAR 75b of April 2007)

Type: Preliminary Cost-Utility Analysis

Last Updated: July 2008

Appendix 1 –6: Appendices relevant to assessment of the 12 month sequential and 9 weeks concurrent CUAs (TAR75 and TAR75b)

Appendix 7: Clinical Advisory Committee Minutes since publication of TAR 75b in April 2007

Appendix 8: Discussion of updated disease progression and clinical efficacy inputs for CUA

Appendix 9: Updated summary table of the clinical trial evidence for trastuzumab treatment regimens

Rationale for further assessment of trastuzumab in HER-2 positive early breast cancer

Background

Trastuzumab was listed as a nine week course of treatment for HER-2 positive early breast cancer in July 2007.

TAR 75 (August 2006) analysed the cost-effectiveness of funding 12 month sequential treatment with trastuzumab compared to standard treatment. It 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 the HERA trial would result in 12.5 to 14.2 QALY per million net dollars spent by DHBs ($70,000-$80,000 per QALY to Vote:Health), with an unusually wide range of outcomes that did not give enough certainty to determine whether twelve months of sequential trastuzumab was cost-effective.

In TAR 75b (April 2007), the analysis was updated to analyse the effects of funding a concurrent nine week treatment with trastuzumab compared with standard treatment. The analysis of the nine weeks concurrent regimen resulted in a base case (with assumptions that generally favoured standard treatment, i.e. a slightly pessimistic view) of 60 to 65 QALYs per million net costs to DHBs (i.e. $14,500-$16,500 per QALY) at the then current prices for trastuzumab and docetaxel, with a possible improvement to over 90 QALYs per $1 million ($11,000 per QALY) once a generic version of docetaxel became available in future (resulting in a likely price reduction). A direct comparison between 9 weeks and 12 months treatment was not undertaken, as if it were assumed that both regimens provide similar efficacy, then the 9-weeks regimen would clearly dominate twelve months sequential treatment (similar efficacy, lower cost). TAR75b note that 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 remained more cost-effective than the base case result for the twelve months regimen ($57,000 vs. $70-80,000 per QALY).

Following an application by eight plaintiffs for judicial review of PHARMAC's decisions relating to trastuzumab (Herceptin), the High Court ordered that PHARMAC's decision in July 2006 not to fund twelve months treatment with trastuzumab be set aside. The Court directed PHARMAC to reconsider the decision following consultation.

To inform the decision on the funding of 12 months regimen this further supplement to the original CUA updates the model in the following ways:

- includes the 12 months concurrent regimen (which has not previously been explicitly modelled);
- new clinical evidence for all regimens;
- revised baseline disease risks;
- new PHARMAC policies for cost-utility analysis [1]; *and*
- provides further sensitivity analyses for different treatment scenarios.

This document outlines the key changes to the updated model, and summarises the results and sensitivity analyses.

For the current analysis, the various treatment regimens are combined into a single model, allowing for easier and simultaneous comparison. The treatment regimes included are standard care, and both 12 months and 9 weeks concurrent treatment with trastuzumab. Twelve months sequential has not been modelled as it is considered that 12 months concurrent is more effective (see Appendix 7). The previous model (described in TAR 75 and 75b) contained tracker variables that allowed for a more detailed and subtle modelling of treatment effect, however these

trackers also made reporting and amending the model more difficult. In order to easily model a wide range of scenarios the trackers were removed and separate arms for each treatment regimen created. The model was further updated to reflect changes to the Prescription for Pharmacoeconomic Analysis (discount rate), baseline disease progression for HER2 positive early breast cancer (as previously described in TAR 75 and 75b) and new clinical information for health outcomes with treatment with trastuzumab in HER2 positive early breast cancer. Further, a number of issues raised in consultation were tested in the sensitivity analyses of this new model.

Updated Inputs for Cost-Utility Analysis

Key updated inputs in the CUA since TAR75b include:

- discount rate – amended from 8% to 3.5%;
- cycle length – reduced from 6 months to 3 months;
- baseline disease progression;
- comparative effectiveness of trastuzumab regimens;
- duration and durability of benefit;
- cardiotoxicity; and
- costs of treatment.

Structural differences and key changes to the revised analysis

PHARMAC published a new version of the Prescription for Pharmacoeconomic Analysis (PFPA), the document that outlines PHARMAC's methods for cost-utility analysis, in May 2007 [1]. The current model aligns the model structure and inputs with the new version of the PFPA, and these changes are outlined below.

Discount rate

Costs and benefits in the original CUAs (TAR 75 and 75b) were discounted at a rate of 8%, consistent with PHARMAC's policies for CUA at the time (PFPA version 1). Since that time, the new version of the PFPA has been published (version 2) [1], which recommends these analyses use a discount rate of 3.5% in the base case.

The costs of trastuzumab incur upfront, whereas its benefits tend to accrue in the future (from avoided disease events, corresponding to life expectancy gains for some patients). Therefore, decreasing the discount rate would be expected to improve the cost-effectiveness results (decrease the cost per QALY), as life gains in the future have greater effect (are discounted less).

The sensitivity analysis section of the original TAR shows that decreasing the discount rate in the original model from 8% to 3.5% decreases the cost per QALY by 35%. Therefore this analysis is very sensitive to changes in the discount rate. Note however, a number of other amendments to this CUA were also required to model the cost-effectiveness of trastuzumab for HER2 positive early breast cancer. These were identified in Appendix Two to TAR75b, and are further discussed in the remainder of this report.

Amendment 1:
Costs and benefits that occur in the future are discounted at 3.5% rather than 8%.

Time horizon and cycle length

Costs and benefits of treatment were modelled over a lifetime as in previous models. The updated model had a cycle length of three months (or four cycles per year), which fits more consistently with the treatment protocol and increases the reporting capabilities compared with the six month cycle length of the original CUA.

Amendment 2:
Cycle length of model reduced from 6 months to 3 months.

Updated clinical information for cost-utility analysis

The majority of clinical information for this analysis is described previously in the main and supplementary analyses (TAR 75 and TAR 75b) and related appendices. Updated information since that time is detailed in Appendices 7-9 of this report.

Disease progression of HER-2 positive early breast cancer

The original CUA model assumed a faster rate of disease progression for HER2 positive early breast cancer over a 10 year time horizon than that currently observed with standard chemotherapy (see 'Validation of underlying survival in HER2-positive breast cancer', page 35 TAR 75, and Appendix Five TAR 75b). Therefore, the original model overstated the benefit of treatment (treatment with trastuzumab prevented more disease recurrences), and thus favoured the trastuzumab regimens compared with standard care.

The modelling of the disease progression (overall survival) for HER-2 positive early breast cancer not treated with trastuzumab has been amended to be consistent with results from 10 year cancer registry data from Finland (FinProg) [2] and recently published 10 year follow-up adjuvant chemotherapy trial data (Mammary.5) [3,4]. For further information regarding the baseline disease progression curves, see Appendices 7 and 8 attached to this TAR.

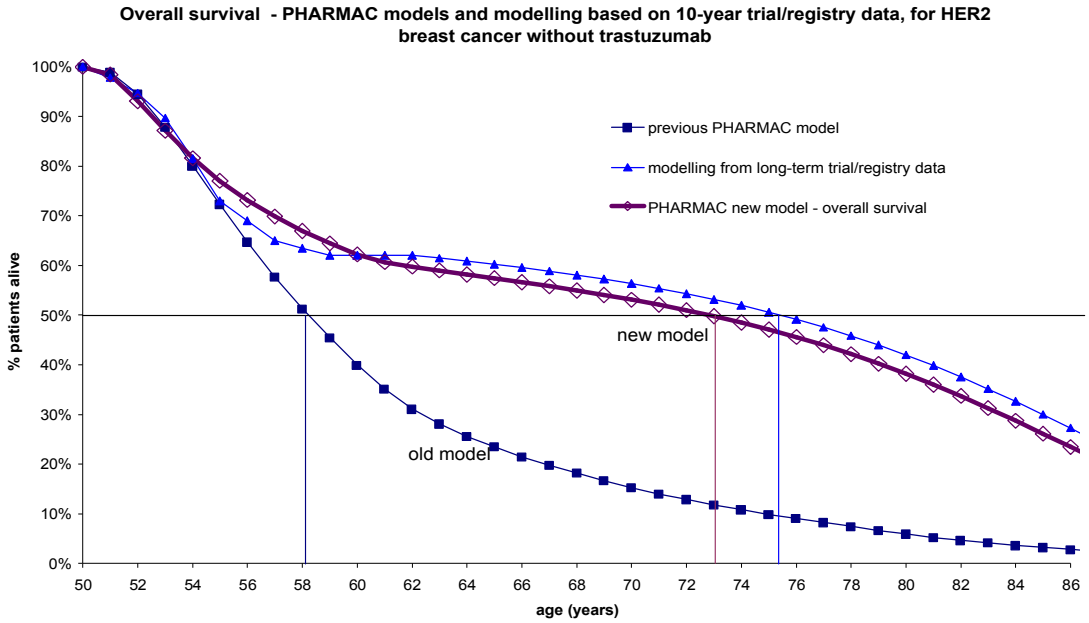
Patients who relapse have been split proportionally amongst the health states for recurrence (local/regional, contralateral and distant) following the proportions reported in 1 year follow up of the HERA trial. These results are similar to those reported in the 2.9 year median follow up of the joint analysis of NSABP-B31 and NCCTG-N9831 concurrent arm [46]. Disease progression from these health states has been extrapolated to fit the known responses to treatment and the overall FinProg overall survival curves.

Amendment 3:
Rate of disease progression associated HER2 positive breast cancer updated with recently published 10-year follow-up data. These data indicate a slower rate of disease progression than previously modelled.

The amended overall survival curve for baseline disease progression is shown in the graph below (graph 1). As the actual long-term overall survival with trastuzumab is unknown, and the updated curve may overstate survival in the longer term, sensitivity analysis on the overall survival curve has been undertaken to determine how changes in expected overall survival affect the results.

Modelling has then back-calculated disease free survival (DFS) and consequent risks for disease progression for standard care, and then applied/overlaid trial-based relative risks to derive DFS for trastuzumab-treated patients with consequent disease risks and overall survival.

Graph 1: Overall survival curves for trastuzumab and standard care



For further information on how these revised baseline risks of disease recurrence were derived, please refer to Appendix 8 of this TAR.

Comparative efficacy of trastuzumab treatment regimens for early breast cancer

Since the last update of analysis (TAR 75b, April 2007), new trials for trastuzumab have become available, and the original trial data has matured with longer term follow-up. Analysis of all the available data provides a more complete picture of the extent of treatment benefit with the differing trastuzumab regimens.

The benefit of trastuzumab treatment is modelled by the implied relative risks for disease free survival (DFS) benefit from the data available from the trials. When more than one result was available for the treatment regimen, standard meta-analysis techniques have been utilised to produce an overall relative risk (RR) result. The updated clinical data, meta-analysis methods and results are further described in Appendix 5 and 6 of this TAR, and the full dataset included in this analysis is summarised in Appendices 7 to 9.

The DFS RR for the different trastuzumab regimens are shown in the table below (table 1). Calculated overall RR have been used for the base case analysis of each regimen (with the exception of the nine weeks analysis, which is described further below), and subjected to sensitivity analysis with the comparative 'worst-case event' RR to reflect the risk associated with the central estimate (using upper limit of the 95% confidence interval).

Note that the FinHer central estimates for disease progression events are better than those of overall 12 month concurrent treatment (45% RR at three years (HR 0.42)). However, similar to the previous CUA, modelling for the base-case analysis conservatively assumes no difference in efficacy between the two regimens in the first three years, and hence applies the rates for 12 months concurrent treatment to nine-week treatment (rather than using FinHer's central estimates). Therefore, using the 12 month concurrent transition probabilities may be a conservative estimate of treatment benefit, and as such the base case model may understate the cost-effectiveness of the nine week concurrent regimen.

In order to more accurately model the observed absolute risk reductions the RRs were used (note: previously hazard ratios were used). Base case relative risks used in the analyses were 0.75 for 12 months sequential and 0.6 for 12 months concurrent and 9 weeks concurrent regimens. For comparative 'worst case' sensitivity analyses, RRs were 0.85, 0.67 and 0.84 for 12 months sequential, 12 months concurrent and 9 weeks concurrent regimens respectively (from the calculated upper 95% confidence limits for the overall RRs).

Table 1: Previous and updated relative risks of different trastuzumab treatment regimens

	Base case disease event % RRR* (HR, RR)	**'Worst case' disease event % RRR* (HR, RR)**
Previous Model		
12 months sequential	46% (0.54)	N/A
9 weeks concurrent	46% (0.54)	17% (0.83)
Updated model		
12 months sequential	28% (0.72, 0.75)	22% (0.78, 0.85)
12 months concurrent	47% (0.53, 0.60)	40% (0.60, 0.67)
9 weeks concurrent	47% (0.53, 0.60)	17% (0.83, 0.84)

*where "RRR" is based on hazard ratios (1-HR), not relative risk

The benefit of trastuzumab treatment is modelled by applying the relative risks baseline disease progression rate in the trastuzumab treatment arms. This method gives 3 year absolute risk reductions that are greater than reported for the 12 month concurrent regimens - this favours the 12 month concurrent trastuzumab regimen.

The appreciable difference in the RR for the sequential regimen in this analysis is due to data from two further studies becoming available since the original analysis was undertaken. These studies are Arm B (sequential) of NCCTG-N9831 [5,6] and PACS04 [7,8], and both show relatively smaller and statistically non-significant differences in DFS when 12 months of trastuzumab is added to standard care than has been shown in the other study of 12 month sequential treatment (the HERA trial). These data have been combined by meta-analysis to give an overall RR for the sequential regimen of 0.75. Further, PTAC considers that sequential treatment may be a less effective use of the agent in treating HER2 positive breast cancer. For further information on Arm B of N9831 and PACS04, or the calculation of the overall RRR, see Appendix 8 to this TAR75C.

Amendment 4:
Updated RR information for each regimen was calculated using all the available information and incorporated into the model for each regimen.

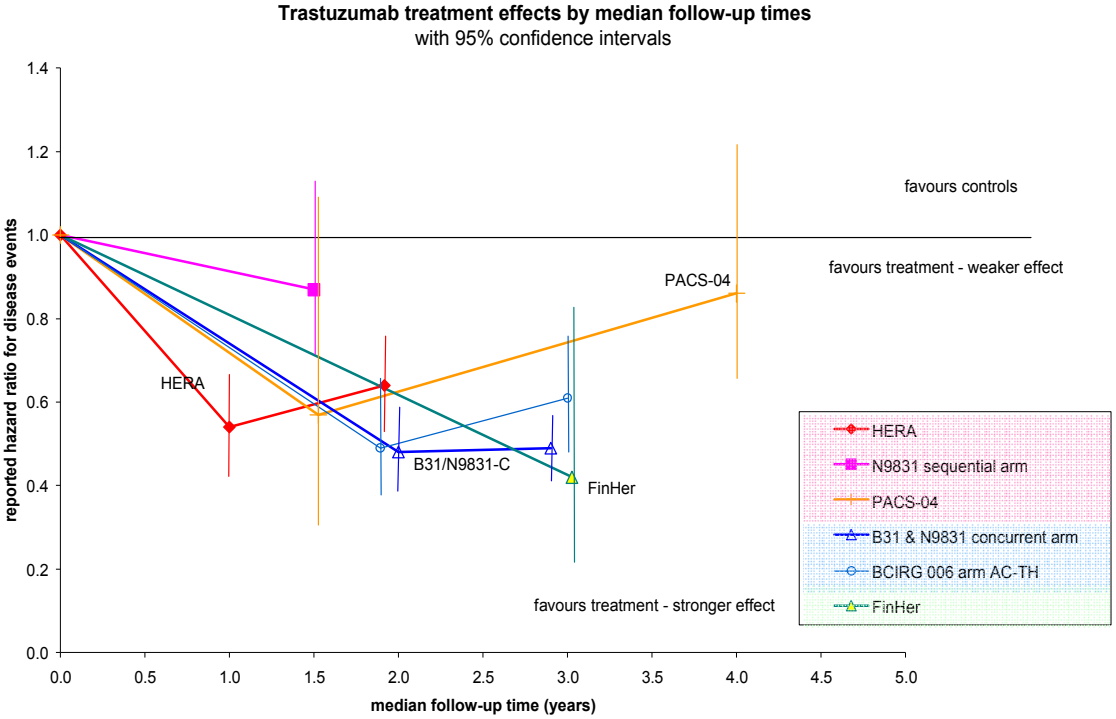
For further information on how these relative risks were derived, please see Appendices 7- 9 to this TAR.

Duration and durability of response to trastuzumab

The original analysis for 12 months sequential treatment (TAR 75, August 2006) assumed the initial response rate for the HERA trial was maintained for four years, after which patients adopted the baseline risk for disease progression. Since that time, longer-term follow-up data have become available, and the model has been updated to fit these long-term follow up data. Analysis of all the available clinical data for trastuzumab, including longer-term follow-up data for the differing trastuzumab regimens, appears to show a waning of treatment effect, especially for the 12 months

sequential regimen. This is depicted in the graph below, which shows the central HR estimate increasing over time.

Trends in HRs with 95% CIs for disease events by median follow-up time for individual trials (including 95% CIs)



Notes to figure:

- The effectiveness of 12 months concurrent appears to significantly decline in effect over time, as does sequential. HERA was the first to show a possible waning of effect, where the hazard ratio increased significantly from 0.54 at 12 months median follow-up interim analysis to 0.64 at 23 months, p =0.01.

- A similar pattern appears for 12 months concurrent treatment, with apparent statistically-significant decline in effect for BCIRG006 arm AC-TH (HR 0.49 at 23 months median f/u, 0.61 at 36 months median f/u; $p < 0.01$. Although by contrast the HRs for the joint analysis of trials B31 and N9831 concurrent 12 month treatment indicate that DFS remained unchanged over the same time (0.48 at 2 years median f/u, 0.49 at 3 years, $p = 0.16$), extending to combined all trials of concurrent 12 month regimes (B31, N9831 concurrent, BCIRG006 concurrent anthracyclines) appear to show an overall decline in effect at three years compared with two years median follow-up (incremental relative risks 0.52 vs. 0.77, $p = 0.004$). In short, the significant waning of effect in BCIRG006 appears to dominate the lack of decline (maintained effect) in B31/N9831-concurrent joint analysis, suggesting that the effects of 12 month concurrent treatment too wanes with time.

- FinHer (concurrent 9 weeks treatment) has yet to report further follow-up data beyond its interim 3-year median follow-up results. There is no evidence of statistically significant changes in effect over these three years.

Intention to treat analysis

All patients who receive trastuzumab are assumed to receive the benefits of treatment, which aligns the model with the intention-to-treat population assessments reported in the clinical trials.

Modelling the known benefit

PTAC considered that the short term response to trastuzumab treatment should be modelled as reported by the clinical trial data for the initial three years after the completion of trastuzumab treatment, as there is good clinical trial evidence to this time point. Therefore, the benefit of treatment is modelled by relative risks for the first three years as reported for the clinical trials.

Modelling the extrapolated benefit: medium term

PTAC noted that the durability of clinical benefit with trastuzumab is largely unknown, however that the longer term follow-up data suggests that the DFS curves do not continue to diverge and the clinical benefit appears to be decreasing over time. PTAC has advised that the base case analysis should model some waning of treatment benefit.

The updated base case therefore assumes a medium-term benefit scenario, where some of the benefit of trastuzumab remains in the medium term but is not long lasting, and the relative risk of disease progression increases towards 1 (the baseline risk for disease recurrence, and represents no treatment benefit). To model this effect, some patients are moved into the placebo arm after three years and adopt the placebo risk of progression from this time period. Modelling assumes different rates of waning of effect following the 3 year initial period, depending on the regimen: for 12 months concurrent and sequential regimens, modelling assumes relative risks reach 1.0 at year 10 (i.e. 7 years after the end of the 3 year period-of-known-full-benefit); for the nine weeks concurrent regimen, modelling assumes relative risks deteriorate faster to reach 1.0 at year 6-7 (i.e. 3.5 years after the end of the 3 year period-of-known-full-benefit).

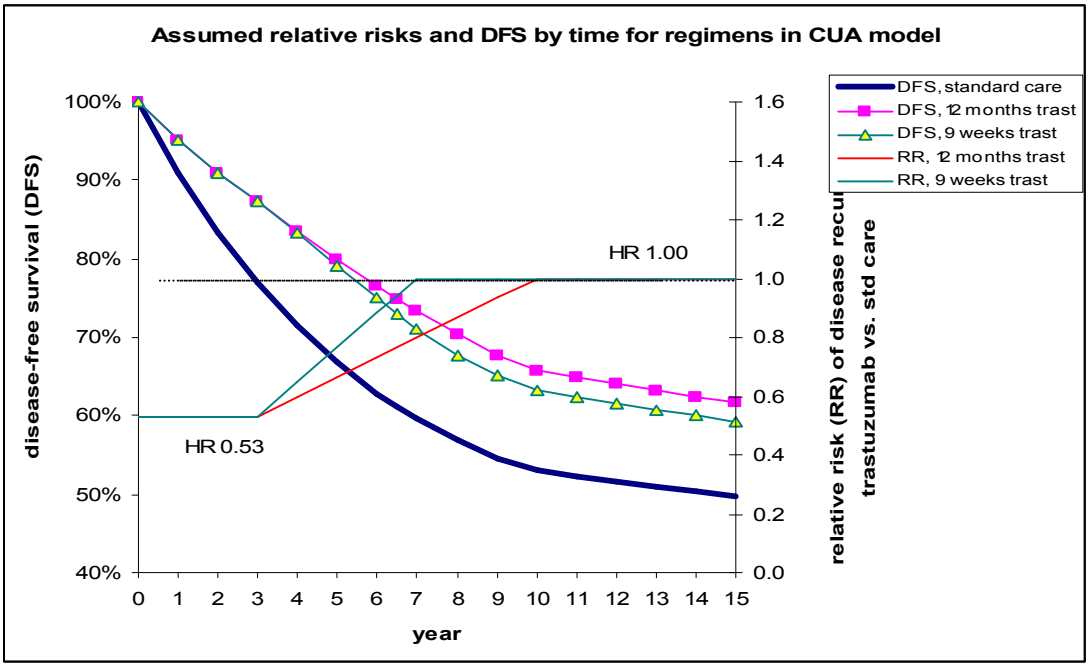
The above scenario models higher benefits than an analysis where the curves would remain parallel, and catch- up disease events (where the curves would converge), but a lower level of benefit than consistent relative risk reduction rates (where the curves would diverge). This assumption has been held across all three scenarios in the base case (note this is an optimistic assumption for sequential treatment). Vigorous sensitivity analyses have been conducted on this particular assumption, and these are described in more detail in the sensitivity analysis section.

Modelling the extrapolated benefit: long term

Patients who remain in the remission state for 10 years (40 cycles) are assumed to adopt baseline disease rates at this time (i.e. these patients are now at no higher risk for breast cancer compared with the normal population who have never had breast cancer). A number of scenarios for modelling the extrapolated benefit have been tested in the sensitivity analysis.

Amendment 5:
The short-term response to trastuzumab was based on the clinical trials for the initial three years after completion of treatment. This data was then extrapolated, assuming waning of effect over time (relative risk of disease recurrence increases towards 1). Patients in remission after 10 years were assumed to no longer be at higher risk of breast cancer than the normal population.

Relative risks for disease events and consequent DFS are therefore modelled over time for treatment regimens as follows:



For further information on how these revised baseline risks of disease recurrence were derived, please see Appendix 8 to this TAR.

Cardiotoxicity

Based on relevant material published since mid 2007 on cardiotoxicity, including reversibility [9-14], the model assumes the following cumulative incremental rates of symptomatic heart failure and severe cardiac events as reported in the clinical trials for the treatment regimens (rates incremental to those reported for standard care).

Table 2: Cardiotoxicity Rates

Treatment regimen	Symptomatic congestive heart failure	Severe cardiac adverse effects
12 months sequential post AC	1.13%	0.54%
12 months concurrent post AC	6%	3%
9 weeks concurrent pre-AC	1.13%	0.54%

Previously (in TAR75b) it was assumed that adverse effects in the nine weeks concurrent regimen would occur at the same rate as in the 12 months sequential model, for the first six months of treatment, in effect meaning the incidence of adverse effects was reduced by half compared with the 12 months sequential model.

Cardiac events reported in the FinHer trial may have been comparatively low because of possible artefact (underpowered to detect and measure cardiac toxicity; lessened sensitivity (LVEF detection); lower than standard doses of epirubicin), rather than nine-week concurrent regimen being truly less cardiotoxic than long duration regimens. Pending further data, the updated model therefore now assumes the rates of adverse cardiac effects for the nine weeks concurrent regimen to be the same as those reported for the 12 months sequential regimen. This assumption is conservative, disfavouring the nine week concurrent trastuzumab regimen.

Asymptomatic decreases in LVEF have not been modelled for this updated analysis because these are not classified as severe, would potentially not be identified in clinical practice due to the asymptomatic nature, and appear to be reversible on cessation of treatment. If the prevalence of asymptomatic decreases in LVEF, and a treatment protocol for the management of this condition, were to be included in the

analysis this would disfavour the concurrent 12 months regimen (where in the NSABP-B31 trial 34% of patients treated with trastuzumab experienced decreases in LVEF, compared with 17% of patients in the standard chemotherapy arm).

Sensitivity analyses modelled increased rates of cardiotoxicity, to reflect the likelihood that some patients treated in clinical practice in New Zealand would have poorer baseline heart function and pose higher risks for cardiotoxicity (not having met the strict inclusion criteria for the clinical trials). This assumption disfavours trastuzumab, especially the 12 months concurrent regimen, hence modelled in the sensitivity analysis rather than the base case.

The CUA model does not adjust for different patient numbers receiving trastuzumab treatment with the different regimens. Conceivably, more patients may be able to receive treatment with the nine week concurrent regimen than the longer duration regimens, due to possible lower cardiotoxicity from it being given before anthracycline treatment as per the FinHer protocol. This is a conservative assumption (favours 12 months treatment).

***Amendment 6**:*
The analysis included the higher rate of cardiotoxicity associated with the 12 months concurrent regimen (the original CUA was based the rates of adverse effects on the 12 months sequential HERA trial).

For further information on trastuzumab-associated cardiotoxicity, please see Appendix 8 to this TAR.

Updated Costs

Cost of trastuzumab

Compared with previous models, a higher cost of trastuzumab was used for the base case. The cost included for trastuzumab the ECP cost ($9.36 per mg for injection), with an additional cost for compounding of 5%. For the 12 month arm a price reduction according to the commercial proposal received was modelled (the effective price being commercial-in-confidence).

The effect of different price decreases for 12 months concurrent trastuzumab, with the nine week regimen held constant, is modelled in the sensitivity analysis.

Amendment 7:
Cost of trastuzumab amended to more accurately reflect the ECP cost, additional costs for compounding, and proposed price reduction for the 12-month regimen.

Cost of taxane chemotherapy

Paclitaxel was used for the 12 months regimen (most of the clinical trials for 12 months used paclitaxel for taxane chemotherapy). Docetaxel was used for the nine weeks concurrent regimen, as per the FinHer regimen for the clinical trial and nine week concurrent regimen currently funded in New Zealand. Consequently, paclitaxel use was included for the 12 months regimens, at a cost of $1,700, and docetaxel was included for the nine weeks concurrent regimen at a cost of $12,000. The docetaxel cost was varied in the sensitivity analysis to determine the effect of expected generic entry.

Cost of treatments for metastatic breast cancer and palliative care

The base case analysis assumed the costs of metastatic breast cancer (distant relapse) and palliative care to be the same as in the original 12 month sequential analysis (cost of distant relapse and cost of terminal care). The effect of increasing the costs of disease recurrence was assessed in the sensitivity analysis.

The base-case analysis assumed the costs of palliative care to be the same as the original CUA for 12 months sequential treatment. These costs were varied (increased) in the sensitivity analysis to determine the effect of higher disease progression costs on the cost-effectiveness of treating early breast cancer patients with trastuzumab.

Markov Model

A diagram of the TreeAge Markov model is included on the next page.

PTAC view

Since the April 2007 supplementary analysis, PTAC and the Cancer Treatment Subcommittee of PTAC (CaTSoP) have reviewed trastuzumab for HER2-positive early breast cancer at various stages. PTAC's July 2008 meeting specifically considered both new data and clinical issues directly relevant to this update of the cost utility analysis.

The relevant PTAC and CaTSoP minutes since TAR75b (April 2007) are included in Appendix 7 to this TAR75c.


12 months Herceptin
3
Dead (Cancer)
Dead (Background Mortalilty)
Local Relapse
(lumpectomy, RT, chemo) (Treatment)
1
Survive
Local relapse
=Local Relapse
Distant relapse
=Distant Relapse
Remission
=Remission
Die Cancer
Dead (Cancer)
Die
Dead (Background Mortalilty)
Local Relapse
(lumpectomy, RT, chemo) (No treatment effect)
Clone 1: Local Relapse
Contralateral
(mastectomy, RT, chemo) (Treatment)
4
Survive
Remission
=Remission
Distant relapse
=Distant Relapse
Die Cancer
Dead (Cancer)
Die
Dead (Background Mortalilty)
Contralateral
(mastectomy, RT, chemo) (No treament effect)
Clone 4: Contralateral
Distant relapse
(chemo or herceptin) (Treatment)
5
Survive
Response
Partial
=Distant Relapse
Total
=Remission
Progressive disease
Palliative care
Stable
=Distant Relapse
Die Cancer
Dead (Cancer)
Die
Dead (Background Mortalilty)
Distant relapse
(chemo or herceptin) (No treament effect)
Clone 5: Distant Relapse
Palliative care
Palliative care
Pallative care
Palliative care
Die Cancer
Dead (Cancer)
Die
Dead (Background Mortalilty)
Total Remission
Survive
Total Remission
Die
Dead (Background Mortalilty)
No treatment effect
Survive
event-free
success
No treatment effect
Event-free
=EventFree
Distant
Distant relapse (chemo or herceptin) (No treament effect)
Contralateral
Contralateral (mastectomy, RT, chemo) (No treament effect)
Local relapse
Local Relapse (lumpectomy, RT, chemo) (No treatment effect)
Die Cancer
Dead (Cancer)
Die
Dead (Background Mortalilty)
Treatment
Survive
No Adverse Effects
event-free
Continued additional risk of BC
Continued treatment benefit
Treatment
Discontinued treatment benefit
=Tunnel Crossov
Total Remission
=EventFree
Distant
Distant relapse (chemo or herceptin) (Treatment)
Contralateral
Contralateral (mastectomy, RT, chemo) (Treatment)
Local relapse
Local Relapse (lumpectomy, RT, chemo) (Treatment)
Die Cancer
Dead (Cancer)
Adverse Event
Remission
2
Symptomatic CHF
=event
Other adverse
=event
Infection
=event
Severe cardiac
=event
Survive
Distant
Clone 2: Side effects
Contralateral
Clone 2: Side effects
Local relapse
Clone 2: Side effects
Die Cancer
Dead (Cancer)
Die
Dead (Background Mortalilty)

Cost-Utility Analysis Results

Incremental cost-effectiveness of the 12 months concurrent regimen compared with the 9 weeks concurrent regimen

A cost-utility analysis has been undertaken to calculate the cost-effectiveness of the 12 months concurrent regimen compared with the nine weeks concurrent regimen of trastuzumab for early HER2 positive breast cancer. If, as the evidence suggests, nine weeks is as effective as 12 months, then the nine weeks concurrent treatment regimen dominates the 12 months regimen (ie. produces the same, or greater, benefits at a lower cost). Given the uncertainty surrounding the benefits of trastuzumab in this indication, extensive sensitivity analysis has been undertaken.

Alternative scenario: a lower efficacy of nine weeks treatment

The base-case sensitivity analysis has addressed the key question: "what if the benefits of nine weeks concurrent treatment are less than reported, and less than the benefits of the 12 months concurrent?" This sensitivity analysis assumes reduced the efficacy for nine weeks trastuzumab.

There are two factors contributing to DFS and OS benefit with trastuzumab: the RR of disease recurrence (or short term benefit to three years, as informed by the clinical trial data), and the duration of treatment benefit (how long the benefit lasts, and how quickly it wanes).

Therefore, this sensitivity analysis has included the following pessimistic assumptions with regard to the effect of the nine weeks concurrent regimen:

- RR for disease recurrence (short term benefit) reduces to model nine weeks at the same efficacy as the 12 months concurrent treatment (RR 0.60) in the first three 3 years, and
- A greater, or more aggressive, waning of treatment effect (shorter duration of treatment benefit) than 12 months concurrent.

Under these assumptions, the cost per quality adjusted life year (QALY) of 12 months concurrent compared with nine weeks is over $100,000 (less than 10 QALYs per $1 million invested).

Cost-effectiveness of 12 months concurrent compared with standard care

Further sensitivity analysis has been undertaken to determine the incremental cost effectiveness of 12 months concurrent in the absence of the nine weeks concurrent regimen. In effect, this scenario addresses the question: "what if nine weeks is ineffective?" This sensitivity analysis has compared the 12 months concurrent regimen with standard care (no trastuzumab treatment). As explained previously, this analysis does not consider the sequential regimen (as had been previously modeled), as sequential treatment is considered to be less effective than concurrent.

Table 3: Cost-effectiveness of 12 months concurrent regimen compared with standard treatment

	Result
Incremental Average Life Expectancy	2.6 years[†]
Incremental QALYs	1.5
Incremental Costs	$63,000
Incremental Cost per QALY	$35,000 - $50,000
QALY's gained per $1m invested	20-29

[†] Undiscounted

The CUA result for this analysis is approximately $40,000-$55,000 per QALY, and decreases to $35,000-$50,000 per QALY over 4 years as the effects of future reductions in the price of trastuzumab are included.

Given the lack of long term data the above result is optimistic. In a more conservative scenario with a faster waning of effect, i.e. if it is assumed that the waning of effect happens at twice the rate (i.e. the same as assumed for nine weeks concurrent regimen) the cost per QALY is approximately $45,000 - $60,000[i] (17-22 QALYs per $1 million invested). If a stop and drop approach is assumed (no benefit of trastuzumab beyond the follow up period reported by the clinical trials), the cost per QALY is approximately $55,000 - $75,000[i] (13-18 QALYs per $1 million invested).

Cost-effectiveness of 9 weeks concurrent compared with standard care

Further sensitivity analysis of the cost-effectiveness of nine weeks trastuzumab compared with standard care (no trastuzumab treatment) has shown that, with pessimistic assumptions regarding to the efficacy of the nine weeks regimen, the incremental cost per QALY is approximately $10,000-$25,000 (40-100 QALYs gained per $1 million invested). This range includes the results that have previously been reported for the 9 weeks treatment regimen. In this scenario the effect of using a lower discount rate of 3.5%, where the previous analysis used 8% are negated by the pessimistic assumptions with regards to the efficacy of the nine weeks regimen.

Table 4: Cost-Effectiveness of 9 weeks concurrent regimen compared with standard treatment (with assumptions disfavouring nine weeks treatment)

	Result
Incremental Average Life Expectancy	2.2 years[†]
Incremental QALY's	1.2
Incremental Costs	$23,000
Incremental Cost per QALY	$10,000 - $25,000
QALY's gained per $1m invested	40-100

[†] Undiscounted

If the reported 3 year relative risk for 9 weeks regimen (RR 0.45) is used the cost per QALY is approximately $8,000 - $15,000 (67-125 QALYs gained per $1 million invested).

[i] These scenarios are calculated with the lower future price of trastuzumab, based on Roche's bundled commercial offer.

Sensitivity Analysis

This section focuses on challenging key assumptions in the model, and how changes in these inputs affect the cost-effectiveness result. A key point to note is that some of the scenarios tested are extreme, and therefore the spectrum of results reported does not represent the plausible range for the base case analysis.

Key Sensitivity Analyses

A discussion of the sensitivity of the results to changes in the following inputs/assumptions is discussed for each model.

Extent of treatment benefit

The upper limits of the confidence intervals have been used to model scenarios with decreased trastuzumab efficacy, i.e. treatment does not decrease the risk of recurrence as much as reported in the initial trials, or the relative risk is closer to 1 (no treatment effect). The confidence interval for the nine week regimen (based on the FinHer trial results) is wider than that for the other regimens, and therefore there is more uncertainty in this result. Therefore, the 'worst case scenario' from the range of the confidence intervals was used to model a lower treatment effect. The relative risk reductions for the different treatment regimens are 0.67 and 0.84 for the 12 months concurrent and nine weeks concurrent regimens, respectively.

Duration of treatment benefit

There is limited evidence for long term treatment outcomes with trastuzumab, and the available evidence suggests some waning in the overall effect with time. The base case analysis has assumed some waning of treatment effect, and has assumed a more aggressive waning of the nine weeks concurrent regimen than for the 12 months regimens. The details of this assumption are further described in the 'duration and durability of response to trastuzumab' section. This assumption favours the 12 month regimens and this has been deliberate – with the intention to model greater certainty for the 12 months regimens (there are more data), and more uncertainty with the nine week regimen (where information is limited to events from one clinical trial with a consequent greater standard error, albeit a better result for central effect).

The scenarios for duration of treatment effect modelled in the sensitivity analysis assumed different scenarios for the extent and duration of trastuzumab benefit. The extent of benefit has been tested in two ways: the initial extent of benefit in the short term (the RR for disease recurrence), and the rate of waning of treatment effect (how long the benefit of trastuzumab lasts). The RR has been varied over the range of results reported in the clinical trials (the 95% confidence interval for DFS benefit). The waning of effect is varied by assuming the relative risk reached 0.8 at year 10, or the relative risk reached 1 part way through year four. The time until waning of effect starts is varied between 2 (one year after completion of treatment) and 10 years (life time benefit).

Discount rate

Given the costs of trastuzumab are incurred upfront (within the first year), and the benefits of treatment are accrued in the future (life expectancy gains from reducing cancer recurrences), this analysis is naturally very sensitive to changes in the discount rate. The cost effectiveness improves (cost per QALY decreases) when the discount rate is reduced because more QALYs are gained (discounted less) relative to the costs.

PHARMAC's discount rate for CUA was decreased from 8% to 3.5% when the new version of the PFPA was approved by the PHARMAC Board in May 2007. Therefore, both the original analysis of 12 months sequential treatment and the 9 weeks concurrent assessment were assessed using the previous 8% discount rate. The current model uses the new 3.5% discount rate for all costs and benefits incurred in

the model, as per the new version of the PFPA [1]. The sensitivity analysis reports the results for discount rates of 0%, 5% and 8% as outlined in the PFPA.

Costs of metastatic breast cancer and palliative care

A sensitivity analysis assumed that patients who had received trastuzumab for early breast cancer would not receive a further course of trastuzumab. This change effectively decreases the cost of metastatic relapse in the treatment arm by 80%. This assumption favours trastuzumab as it increases the cost of metastatic disease in the comparator arm.

The costs of metastatic breast cancer and palliative care have been varied in the sensitivity analysis to determine how disease progression costs effect the cost per QALY of trastuzumab for early breast cancer. The costs of metastatic breast cancer are varied by up to 230%. This sensitivity analysis therefore captures the effect of higher drug treatment costs for metastatic breast cancer (e.g. treatment of metastatic breast cancer with more expensive pharmaceutical treatments than currently included in the model). The costs of palliative care are varied by 50% to determine the effect of different costs of terminal care (eg. higher hospice costs, or higher proportion of patients treated in a hospice, than currently modelled).

Sensitivity analysis on other costs:

Docetaxel: To estimate the effect of expected generic entry (price reduction) in the near future, a possible price reduction of notionally 50% has been included for this variable. Note that the cost of docetaxel is included for the nine weeks concurrent regimen, as per the regimen used in the FinHer trial.[ii] Therefore this change only affects the cost effectiveness of nine weeks regimen.

Other costs in the model: Similar to the sensitivity analysis for the original 12 months model, in most cases the cost inputs have been varied by 20% (+/- 20%), and where there is more uncertainty in the variables it has been varied by 50%.

Expressing Sensitivity Analysis results

Tornado diagrams

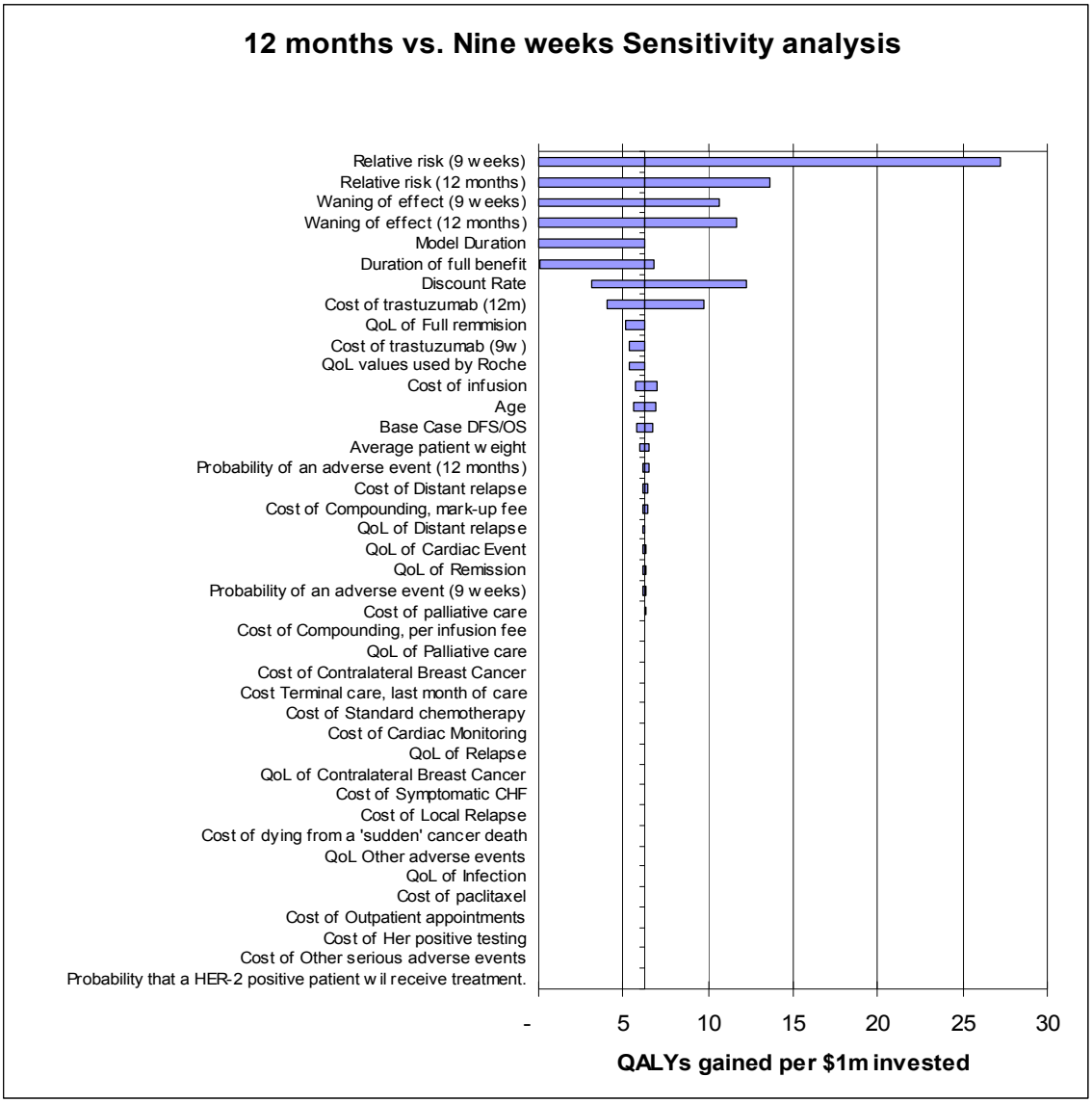
Tornado diagrams graphically display the results of single factor sensitivity analysis. The y axis corresponds to all the uncertain parameters being at their respective nominal, or base, values. The uncertain parameter corresponds to the horizontal bar (the x axis), which is measured in expected QALYs gained per $1 million spend. The parameter associated with greatest uncertainty in the result is reported at the top of the chart, and are arranged in descending order. This gives the graph the 'tornado' appearance for which it is named. These graphs only show limited information (the amount the result changes when a parameter is varied), and do not provide information on how much the parameter needs to be varied to induce the change in the result, or how likely this change is to occur.

Tables

Variables are arranged into similar parameter groups, rather than magnitude of effect, for ease of reference. The tables also show the extent each parameter was varied (high value and low value), and the corresponding result of one-way sensitivity analysis in terms of cost per QALY and its inverse (QALYs gained per $1 million invested).

[ii] It is assumed that paclitaxel would be used for the 12 months concurrent regimen, as per the 12 clinical trials for this regimen.

Alternative scenario: nine weeks less effective than 12 months



The tornado diagram above shows that under most scenarios the QALYs gained per $1million invested are less than 10 (over $100,000 per QALY). Twelve months concurrent treatment was most cost-effective when the expected benefits of the nine weeks regimen were significantly decreased (effectively reduced by more than 50%). Assuming the upper 95% confidence interval limit for the RR of the nine weeks treatment effect (0.84), and the central estimate of effect for the 12 months concurrent regimen (0.60), the approximate result is 27 QALYs per $1million invested. Since this scenario also incorporates a stronger waning of effect for nine weeks compared with the 12 months concurrent regimen, these are pessimistic assumptions for nine weeks that are not supported by the evidence to date. Therefore this scenario is considered to be unlikely.

Table 5: Sensitivity Analysis on trastuzumab 12 months regimen compared with 9 weeks regimen

	Variable	Base Case	Sensitivity Analysis	QALYs gained per $ million	Cost Per QALY
	Base Case				**Over $100k**
Efficacy	Duration of full benefit	3 years	2 years	7	$148,000
			10 years	0	$20,451,000
	Relative risk (9 weeks)	0.6	0.24	0	Dominated
			0.84	27	$37,000
	Relative risk (12 months)	0.6	0.53	14	$73,000
			0.67	0	Dominated
	Waning of effect (12 months)		Half as fast	12	$85,000
			4 times as fast	0	Dominated
	Waning of effect (9 weeks)		A quarter as fast	0	Dominated
			2 times as fast	11	$94,000
	Age	52 years	48 years	7	$146,000
			55 years	6	$178,000
Model Parameters	Average patient weight	71kg	68kg	7	$154,000
			75kg	6	$168,000
	Base Case DFS/OS		10% Higher	6	$173,000
			10% Lower	7	$149,000
	Discount Rate	3.5%	0%	12	$82,000
			8%	3	$323,000
	Model Duration	Life Time	5 Years	0	$101,820,000
	Probability of an adverse event (12 months)		Same as 9 weeks	7	$153,000
			20% increase	6	$162,000
	Probability of an adverse event (9 weeks)		20% decrease	6	$161,000
			20% increase	6	$158,000
	Probability that a HER-2 positive patient wil receive treatment.		0.6	6	$160,000
			1	6	$160,000
	Proportion of patients that are HER-2 positive	0.17	0.125	6	$160,000
			0.25	6	$160,000
Cost	Cost of Cardiac Monitoring		20% decrease	6	$160,000
			20% increase	6	$160,000
	Cost of Contralateral Breast Cancer		20% decrease	6	$160,000
			20% increase	6	$159,000
	Cost of Distant relapse		80% decrease	6	$161,000
			230% increase	6	$155,000
	Cost of Her positive testing		50% decrease	6	$160,000
			50% increase	6	$160,000
	Cost of Local Relapse		20% decrease	6	$160,000
			20% increase	6	$160,000
	Cost of Other serious adverse events		20% decrease	6	$160,000
			20% increase	6	$160,000
	Cost of Outpatient appointments		20% decrease	6	$160,000

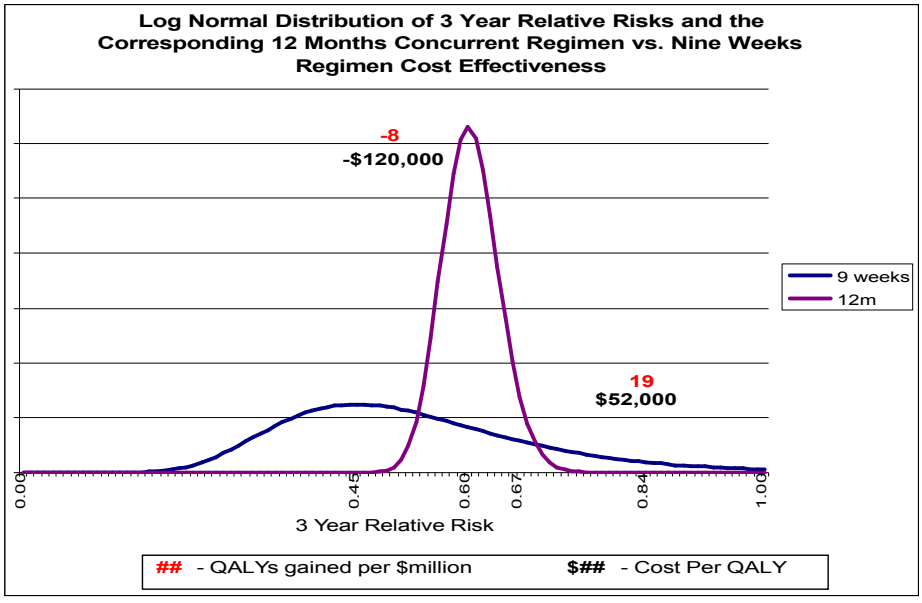
			20% increase	6	$160,000
	Cost of paclitaxel		20% decrease	6	$160,000
			20% increase	6	$160,000
	Cost of palliative care		50% decrease	6	$160,000
			50% increase	6	$158,000
	Cost of Serious Infection		20% decrease	6	$160,000
			20% increase	6	$160,000
	Cost of Standard chemotherapy		20% decrease	6	$160,000
			20% increase	6	$159,000
	Cost of Symptomatic CHF		20% decrease	6	$160,000
			20% increase	6	$160,000
	Cost Terminal care, last month of care		50% decrease	6	$160,000
			50% increase	6	$159,000
	Cost of trastuzumab (12m)	[redacted]	[redacted]	[redacted]	[redacted]
	Cost of trastuzumab (9w)		[redacted]	[redacted]	[redacted]
	Cost of infusion		0	7	$143,000
			100% increase	6	$176,000
	Cost of dying from a 'sudden' cancer death		0	6	$160,000
			50% increase	6	$160,000
	Cost of Compounding, mark-up fee		50% decrease	6	$156,000
			50% increase	6	$163,000
	Cost of Compounding, per infusion fee		33% decrease	6	$159,000
			33% increase	6	$160,000
Quality of Life	QoL of Cardiac Event	0.63	0.4	6	$161,000
			0.84	6	$158,000
	QoL of Contralateral Breast Cancer	0.46	0.36	6	$160,000
			0.56	6	$160,000
	QoL of Distant relapse	0.13	0	6	$159,000
			0.5	6	$161,000
	QoL of Infection	0.78	0.6	6	$160,000
			0.96	6	$160,000
	QoL of Palliative care	0.1	0.04	6	$159,000
			0.2	6	$160,000
	QoL of Relapse	0.46	0.36	6	$160,000
			0.56	6	$160,000
	QoL of Remission	0.85	0.7	6	$161,000
			1	6	$158,000
	QoL Other adverse events	0.83	0.6	6	$160,000
			0.83	6	$160,000
	QoL values used by Roche			5	$187,000

Table 6: Two way sensitivity analysis on treatment benefit

Variables	Base Case	Change	QALYs gained per $Million	Cost per QALY
Base Case				**Over $100k**
Waning of effect (9 weeks)	Twice as fast as 12 months	Same as 12 months	-14	Dominated
Relative risk (9 weeks)	0.6	0.45		
Waning of effect (9 weeks)	Twice as fast as 12 months	Same as 12 Months	24	$41,000
Relative risk (9 weeks)	0.6	0.84		

The first result shows that, if the RRs as reported in the clinical trials are applied for each of the regimens, and the same assumptions are made about duration of effect, nine weeks is more effective and less costly than 12 months concurrent (i.e. nine weeks dominates 12 months). This means that under this scenario investing in 12 months concurrent regimen would result in 14 QALYs forgone per $1 million invested.

The second result evaluates the scenario where the nine week treatment regimen is less effective than 12 months, using the upper 95% confidence interval of the 3 year reported in the FinHer trial (RR 0.84), and the same waning of effect for nine weeks as assumed for the 12 months concurrent regimen.



The diagram above demonstrates the effect of including the range of effectiveness results from the trials (the 95% confidence intervals for DFS from the 3 year follow up of the clinical trials). This incorporates the uncertainty associated with the clinical trial results, and provides the range of cost-effectiveness estimates associated with this uncertainty. Note that this still assumes that the waning of effect is twice as strong for the nine weeks regimen. If the mean relative risks are used, nine weeks is more effective and less costly (dominates the 12 months concurrent regimen). Under this scenario investing in the 12 months concurrent regimen rather than the nine weeks regimen would forgo 8 QALYs per $1 million invested. Using the 95% upper confidence intervals of the relative risks (12 months becomes more effective than nine weeks) the result is approximately 19 QALYs gained per $1million ($52,000 per QALY).

Further discussion of sensitivity analysis results for 9 weeks compared with 12 months concurrent treatment

The diagrams and tables above show that the results of this analysis are reasonably insensitive to changes in most of the inputs.

Extent of benefit of trastuzumab

This analysis is most sensitive to changes in the relative risks of the regimens under assessment, specifically decreasing the expected effectiveness of the nine weeks regimen and increasing the expected effectiveness of the 12 months regimen. There are three variables in the model which correspond to treatment benefit – the relative risk of cancer recurrence imparted by trastuzumab, how long this initial benefit lasts, and rate of the waning of treatment effect.

Model Duration

A shorter model duration means that the effects of trastuzumab are not as long lasting. In the sensitivity analysis the model duration is set to 5 years. This means that after 5 years patients have the same levels of disease free survival (DFS) and overall survival (OS) (i.e. the DFS and OS suddenly converge). Since a lot of the modelled benefit of trastuzumab is improvement in life expectancy, this radically reduces the QALY gains for both treatment regimens.

Using a 5-year model duration (time horizon) radically decreases the cost-effetiveness of the 12 months regimen compared with the nine weeks regimen. This is because the majority of QALYs gained with trastuzumab are expected to occur in the future, with increased life expectancy, and with a five year time horizon the majority of these QALYs have not yet been realised.

Discount Rate

As previously mentioned, the model is expected to be sensitive to the discount rate. As the discount rate is increased the QALY gains in the future are reduced while there is little effect on the incremental cost (which occurs upfront and is not discounted). As there are greater costs associated with the 12 months regimen, the cost-effectiveness of 12 months decreases faster than nine weeks. This results in the cost effectiveness of 12 months compared with nine weeks decreasing as the discount is raised.

Price of trastuzumab

As would be expected, a reduction in the cost to treat with trastuzumab improves the cost-effectiveness. Because trastuzumab is a larger proportion of the costs in the 12 months regimen than in the nine weeks regimen, the effect of a price reduction for the 12 months regimen is associated with a greater improvement in cost-effectiveness than the same price reduction for the nine weeks regimen.

Incremental cost-effectiveness of 12 months concurrent treatment compared with standard care

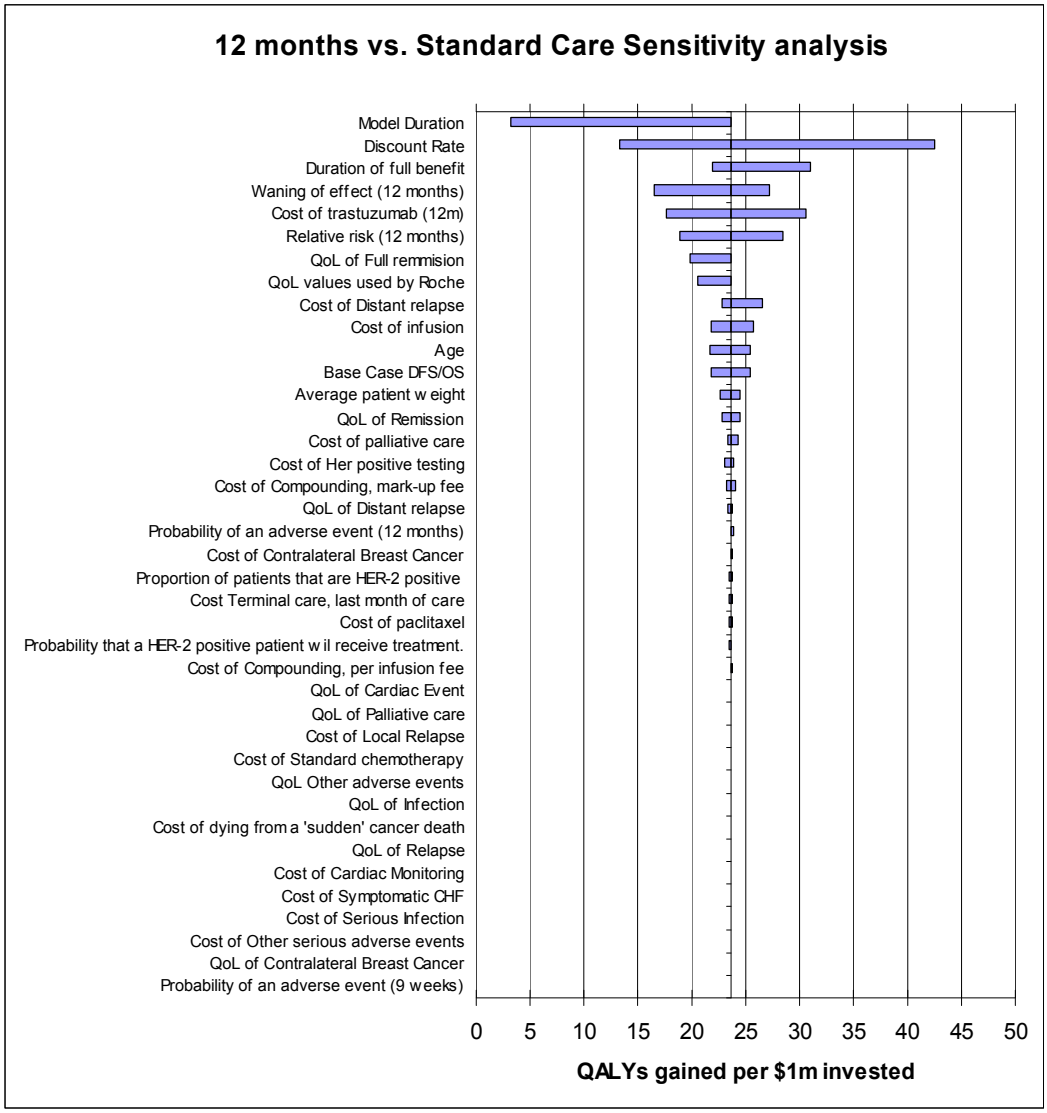


Table 7: Sensitivity analysis on 12 months trastuzumab regimen compared with standard care

	Variable	Base Case	Sensitivity Analysis	QALYs gained per $ million	Cost Per QALY
	Base Case				**$35k - $50K**
Efficacy	Duration of full benefit	3 years	2 years	22	$46,000
			10 years	31	$32,000
	Relative risk (12 months)	0.6	0.53	29	$35,000
			0.67	19	$53,000
	Waning of effect (12 months)		Half as fast	27	$37,000
			4 times as fast	16	$61,000
	Age	52 years	48 years	25	$39,000
			55 years	22	$46,000
Model Parameters	Average patient weight	71kg	68kg	24	$41,000
			75kg	23	$44,000
	Base Case DFS/OS		10% Higher	22	$46,000
			10% Lower	25	$39,000
	Discount Rate	3.5%	0%	42	$24,000
			8%	13	$75,000
	Model Duration	Life Time	5 Years	3	$319,000
	Probability of an adverse event (12 months)		20% increase	24	$42,000
			Same as 9 weeks	24	$42,000
	Probability of an adverse event (9 weeks)		20% decrease	24	$42,000
			20% increase	24	$42,000
	Probability that a HER-2 positive patient wil receive treatment.		0.6	24	$42,000
			1	24	$42,000
	Proportion of patients that are HER-2 positive	0.17	0.125	23	$43,000
			0.25	24	$42,000
Cost	Cost of Cardiac Monitoring		20% decrease	24	$42,000
			20% increase	24	$42,000
	Cost of Contralateral Breast Cancer		20% decrease	24	$42,000
			20% increase	24	$42,000
	Cost of Distant relapse		80% decrease	23	$44,000
			230% increase	27	$38,000
	Cost of Her positive testing		50% decrease	24	$42,000
			50% increase	23	$43,000
	Cost of Local Relapse		20% decrease	24	$42,000
			20% increase	24	$42,000
	Cost of Other serious adverse events		20% decrease	24	$42,000
			20% increase	24	$42,000
	Cost of Outpatient appointments		20% decrease	24	$42,000
			20% increase	24	$42,000
	Cost of paclitaxel		20% decrease	23	$43,000
			20% increase	24	$42,000

	Cost of palliative care		50% decrease	23	$43,000
			50% increase	24	$41,000
	Cost of Serious Infection		20% decrease	24	$42,000
			20% increase	24	$42,000
	Cost of Standard chemotherapy		20% decrease	24	$42,000
			20% increase	24	$42,000
	Cost of Symptomatic CHF		20% decrease	24	$42,000
			20% increase	24	$42,000
	Cost Terminal care, last month of care		50% decrease	23	$43,000
			50% increase	24	$42,000
	Cost of trastuzumab (12m)	[redacted]	[redacted]	[redacted]	[redacted]
	Cost of infusion		0	26	$39,000
			100% increase	22	$46,000
	Cost of dying from a 'sudden' cancer death		0	24	$42,000
			50% increase	24	$42,000
	Cost of Compounding, mark-up fee		50% decrease	24	$42,000
			50% increase	23	$43,000
	Cost of Compounding, per infusion fee		33% decrease	24	$42,000
			33% increase	24	$42,000
Quality of Life	QoL of Cardiac Event	0.63	0.4	24	$42,000
			0.84	24	$42,000
	QoL of Contralateral Breast Cancer	0.46	0.36	24	$42,000
			0.56	24	$42,000
	QoL of Distant relapse	0.13	0	24	$42,000
			0.5	23	$43,000
	QoL of Infection	0.78	0.6	24	$42,000
			0.96	24	$42,000
	QoL of Palliative care	0.1	0.04	24	$42,000
			0.2	24	$42,000
	QoL of Relapse	0.46	0.36	24	$42,000
			0.56	24	$42,000
	QoL of Remission	0.85	0.7	23	$44,000
			1	25	$41,000
	QoL Other adverse events	0.83	0.6	24	$42,000
			0.83	24	$42,000
	QoL values used by Roche			21	$49,000

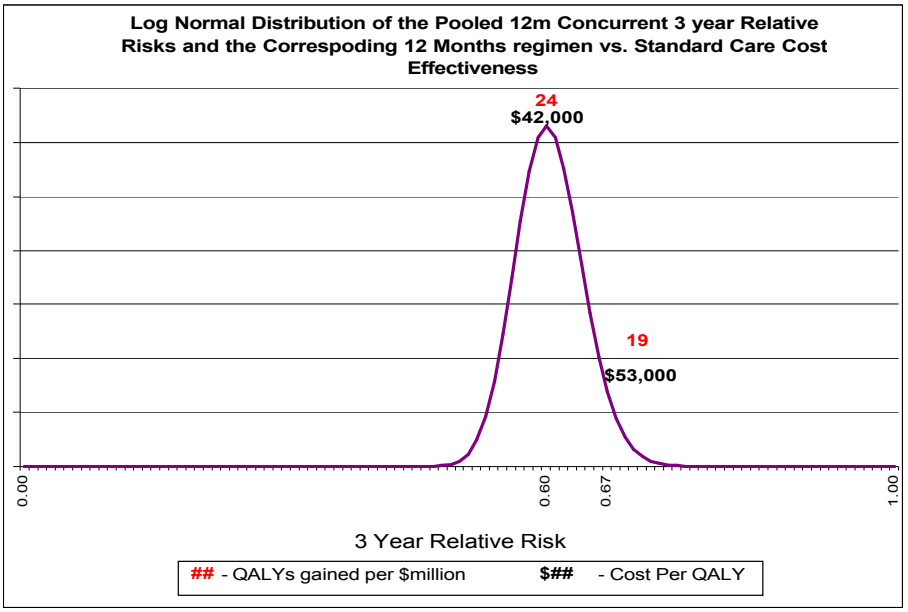
Table 8: Sensitivity analysis around the benefit of effect

Variables	Base Case	Change	QALYs gained per $Million	Cost per QALY
Base Case				$35k - $50k
Waning of effect (12 months)		Half as fast	27	$37,000
		2 times as fast*	19	$52,000
		4 times as fast	16	$61,000

*Same as assumed for nine weeks regimen

Table 9: Further sensitivity analysis around length of benefit

Variables	Base Case	Change	QALYs gained per $Million	Cost per QALY
Base Case				$35k - $50k
Waning of effect (12 months)	Medium term benefit	Life time benefit	31	$32,000
		Short-term	14	$74,000



As the analysis is primarily focused on the results of the comparison of 12 months concurrent compared with the 9 weeks regimen; a discussion of the further sensitivity analysis of 12 month regimen compared standard care has not been included at this stage. A discussion of the sensitivity analysis for the 12 months sequential regimen is included in TAR 75a

Incremental cost-effectiveness of 9 weeks concurrent compared with standard care

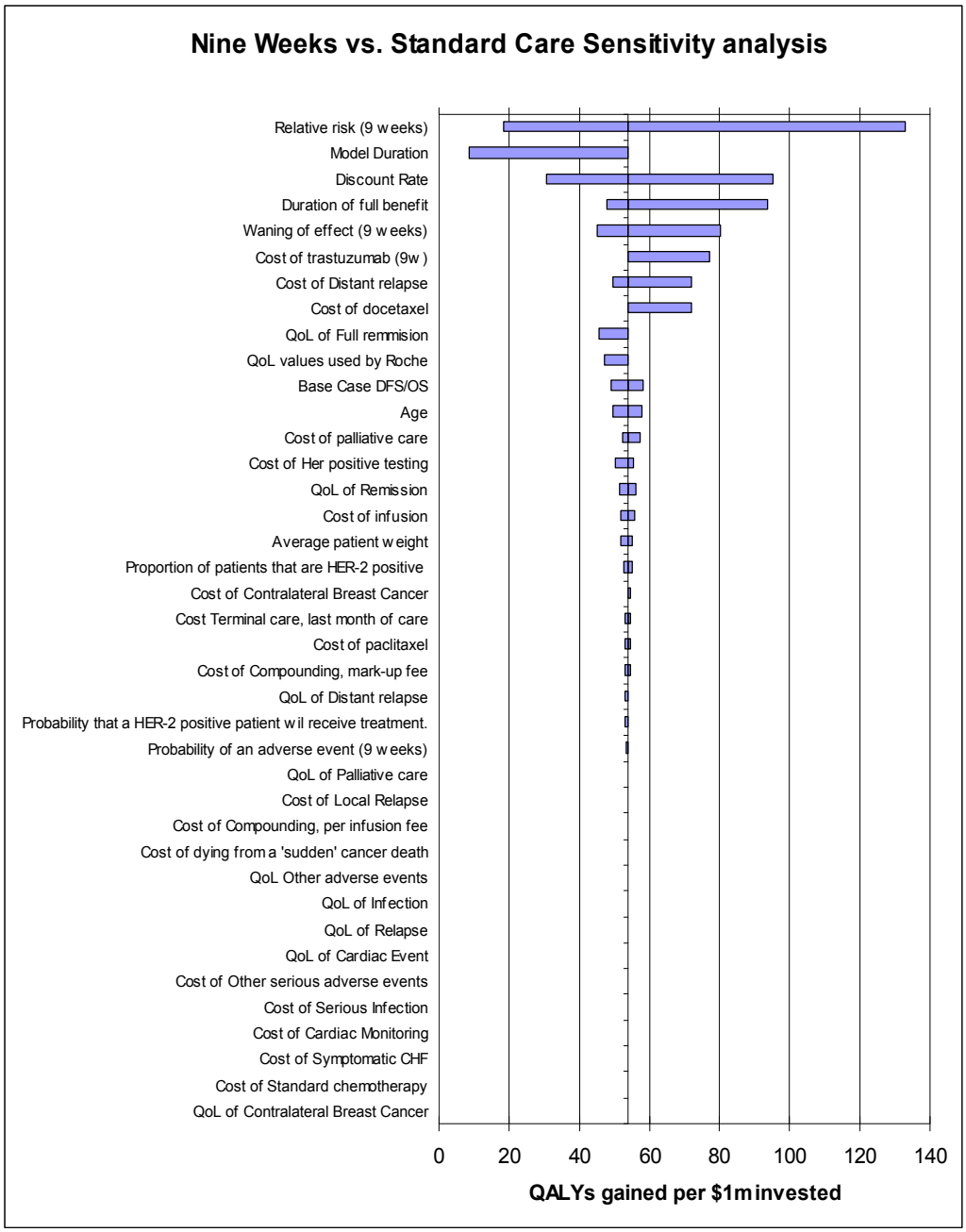
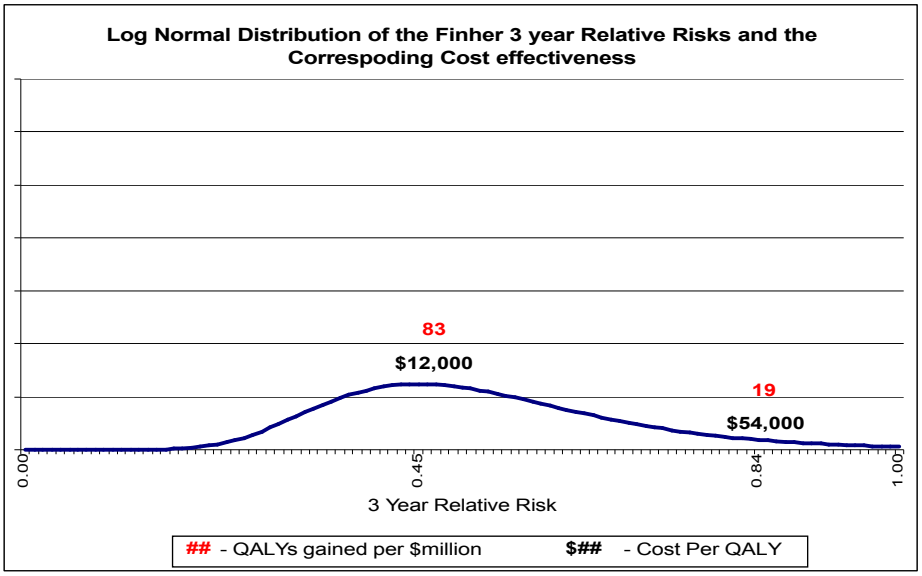


Table 10: Sensitivity analysis on 9-weeks trastuzumab compared with standard care

	Variable	Base Case	Sensitivity Analysis	QALYs gained per $ million	Cost Per QALY
	Base Case				**$10k - $25K**
Efficacy	Duration of full benefit	3 years	2 years	48	$21,000
			10 years	91	$11,000
	Relative risk (9 weeks)	0.6	0.24	125	$8,000
			0.84	19	$54,000
	Waning of effect (9 weeks)		A quarter as fast	83	$12,000
			2 times as fast	45	$22,000
Model Parameters	Age	52 years	48 years	59	$17,000
			55 years	50	$20,000
	Average patient weight	71kg	68kg	56	$18,000
			75kg	53	$19,000
	Base Case DFS/OS		10% Higher	50	$20,000
			10% Lower	59	$17,000
	Discount Rate	3.5%	0%	91	$11,000
			8%	31	$32,000
	Model Duration	Life Time	5 Years	9	$115,000
	Probability of an adverse event (12 months)		20% increase	53	$19,000
			Same as 9 weeks	53	$19,000
	Probability of an adverse event (9 weeks)		20% decrease	53	$19,000
			20% increase	53	$19,000
	Probability that a HER-2 positive patient wil receive treatment.		0.6	53	$19,000
			1	53	$19,000
	Proportion of patients that are HER-2 positive		0.25	56	$18,000
		0.17	0.125	53	$19,000
Cost	Cost of Cardiac Monitoring		20% decrease	53	$19,000
			20% increase	53	$19,000
	Cost of Contralateral Breast Cancer		20% decrease	53	$19,000
			20% increase	56	$18,000
	Cost of Distant relapse		230% increase	71	$14,000
			80% decrease	50	$20,000
	Cost of docetaxel		50% decrease	71	$14,000
	Cost of Her positive testing		50% decrease	56	$18,000
			50% increase	50	$20,000
	Cost of Local Relapse		20% decrease	53	$19,000
			20% increase	53	$19,000
	Cost of Other serious adverse events		20% decrease	53	$19,000
			20% increase	53	$19,000
	Cost of Outpatient appointments		20% decrease	53	$19,000
			20% increase	53	$19,000

	Cost of palliative care		50% decrease	53	$19,000
			50% increase	59	$17,000
	Cost of Serious Infection		20% decrease	53	$19,000
			20% increase	53	$19,000
	Cost of Standard chemotherapy		20% decrease	53	$19,000
			20% increase	53	$19,000
	Cost of Symptomatic CHF		20% decrease	53	$19,000
			20% increase	53	$19,000
	Cost Terminal care, last month of care		50% decrease	53	$19,000
			50% increase	56	$18,000
	Cost of paclitaxel		20% decrease	53	$19,000
			20% increase	56	$18,000
	Cost of trastuzumab (9w)		[redacted]	[redacted]	[redacted]
	Cost of infusion		0	56	$18,000
			100% increase	53	$19,000
	Cost of dying from a 'sudden' cancer death		0	53	$19,000
			50% increase	53	$19,000
	Cost of Compounding, mark-up fee		50% decrease	56	$18,000
			50% increase	53	$19,000
	Cost of Compounding, per infusion fee		33% increase	53	$19,000
			33% decrease	53	$19,000
Quality of Life	QoL values used by Roche		0	48	$21,000
	QoL of Cardiac Event	0.63	0.4	53	$19,000
			0.84	53	$19,000
	QoL of Contralateral Breast Cancer	0.46	0.36	53	$19,000
			0.56	53	$19,000
	QoL of Distant relapse	0.13	0	53	$19,000
			0.5	53	$19,000
	QoL of Infection	0.78	0.6	53	$19,000
			0.96	53	$19,000
	QoL of Relapse	0.46	0.36	53	$19,000
			0.56	53	$19,000
	QoL Other adverse events	0.83	0.6	53	$19,000
			0.83	53	$19,000



As the analysis is primarily focused on the results of the comparison of 12 months concurrent compared with the 9 weeks regimen, a discussion of the further sensitivity analysis of nine weeks regimen compared standard care has not been included at this stage. A discussion of the sensitivity analysis for the 9 weeks regimen is included in TAR 75b.

Discussion

International cost-effectiveness analysis results

There have been several CUAs for trastuzumab in early breast cancer that have been published in the international medical literature. PHARMAC staff have identified 25 reports of analyses (sourced from a Roche NZ January 2008 slide presentation, supplemented by PubMed and TRIP searches 7 July 2008 keywords (trastuzumab AND early breast cancer) AND (economic evaluation OR cost-effectiveness OR cost) [20,22-45]. Some are in poster or abstract form only and as such do not provide sufficient detail for comparative assessment and review.

When key assumptions are held constant, the above PHARMAC analysis results are similar to other published analyses for trastuzumab in early breast cancer, which all report a wide plausible range of results which reflects the uncertainty. Put differently, the results only differ appreciably if the base case model uses different key assumptions (identified below):

- length/durability of treatment benefit (lifetime, or less), and as such the benefit of treatment;
- baseline disease progression;
- discount rate (cost per QALY improves as the discount rate decreases); and
- choice of treatment regimen.

Hence it is not necessarily the results that may be different – it is the choice of assumptions that differs, and drives the results.

As an example of the impact of the underlying evidence and assumptions used, in the UK adjuvant trastuzumab underwent inaugural assessment under NICE's single technology appraisal process, where (contrary to standard appraisals) evidence is provided solely by the supplier [18]. In this instance the FinHer data and the unpublished N9831 sequential arm data [5,6] were not provided [20]. It has been stated that that NICE might never have deemed the 12-month sequential (HERA) schedule to be cost effective had FinHer been assessed as a comparator [21].

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