

## **Appendix 1. Relevant portions of CaTSoP minutes**

### **Record of the Cancer Treatments Subcommittee of the Pharmacology and Therapeutics Advisory Committee Meeting held on 19 April 2006**

#### **Trastuzumab**

The Sub-Committee considered an application from Roche for the use of trastuzumab in early breast cancer. The Sub-Committee noted that this had been considered previously by PTAC and that it was referred to CaTSoP following Medsafe approval.

The Sub-Committee noted that the major evidence for trastuzumab was the HERA trial (N Engl J Med. 2005 Oct 20; 353(16): 1659-72.), and that the application from Roche also included the paper by Romond et al (N Engl J Med. 2005 Oct 20; 353(16): 1673-84.). Members noted that data presented by Romond et al is limited to assessing trastuzumab concomitant with paclitaxel after an anthracycline-containing regimen.

The Sub-Committee noted that the HERA trial was a large, unblinded multi-centre trial examining the use of trastuzumab following chemotherapy with a variety of pre-specified regimens usually (94% of patients) including anthracyclines, and often (25% of patients) including taxanes. Members noted that the results included in the application were from a preliminary analysis, and that further follow-up data, including a two-year treatment arm, would be available later.

Members noted that the Romond paper was a pooled analysis of the B-31 and N9831 trials, and agreed with the comment by PTAC that it would have been preferable to have these two trials presented separately.

The Sub-Committee considered that while the Romond paper provided some beneficial information in addition to the HERA trial, other papers were also relevant, such as the FinHer trial (N Engl J Med. 2006 Feb 23; 354(8): 809-20) and BCIRG 006 study. Members noted that the unreported arm of the N9831 trial would be of particular interest when available.

The Sub-Committee noted that there are currently access issues around the country in relation to both radiotherapy and chemotherapy infusion services. Members considered that waiting times associated with chemotherapy would be likely to increase if trastuzumab was made available for early breast cancer.

The Sub-Committee noted that the preliminary results of the HERA trial indicated a benefit in disease-free survival, but as yet no improvement in overall survival

Members noted new preliminary data provided by Roche comparing concurrent trastuzumab and taxane therapy with a sequential regimen. Members noted that these data appeared to indicate that sequential treatment may not perform as well as a concurrent treatment, although the data are too premature to draw reliable conclusions.

The Sub-Committee noted the increase in the risk of severe (NYHA grade III-IV) heart failure in the patients treated with trastuzumab in the HERA trial and in the paper by Romond et al. Members noted that the risk increase was significantly higher in the Romond paper than in the HERA trial, and considered this difference was likely to relate to the period of time between concluding anthracycline treatment and starting administration of trastuzumab.

Members noted that the cardiac side effects of trastuzumab appeared to be small and manageable, although noted that in the HERA trial there were a number of patients that remained on cardiovascular medication even after normalisation of the LVEF. Members further noted although the cardiac side effects appeared manageable in the short term, the extent of the effects beyond two years remained unknown. The Sub-Committee considered that there would be resourcing issues in hospitals for monitoring cardiac function with echocardiograms.

The Sub-Committee noted that currently most experience with trastuzumab is in the metastatic setting. In this situation, the high mortality rate means that most patients die before severe cardiac adverse effects arise. Members noted that in early breast cancer, at least 50% of patients are expected to survive to 10 years, all of whom would have been exposed to a currently unknown risk of cardiac toxicity.

Members noted that the strict entry criteria in the clinical trials may not be fully adhered to in clinical practice, resulting in patients with higher baseline heart failure risk being treated with trastuzumab. Therefore in practice the increased risk of heart failure could be higher than noted in the clinical trials. Similarly, the Sub-Committee considered that the strict withdrawal criteria in the HERA study might not be followed in practice, resulting in patients continuing with trastuzumab despite decreases in LVEF, symptomatic or otherwise.

The Sub-Committee noted the results of a sub-analysis (232 of 1,010 patients) of the FinHer study, examining the use of trastuzumab for nine weeks post chemotherapy. Members noted that in this small sample, a disease-free survival advantage was demonstrated without any significant increase in heart failure, although the study may not have been powered to detect such an increase.

The Sub-Committee noted that at present there is insufficient evidence to prove the existence of an overall survival advantage with trastuzumab. Members noted that there was a benefit demonstrated in the Romond analysis, but that this was based on the follow-up of relatively few patients. Members noted that the available follow-up for the HERA trial was very short, and as yet there is no overall survival advantage demonstrated.

The Sub-Committee was asked by PHARMAC staff to consider the ability to extrapolate the disease-free survival data from the HERA trial beyond two years. The Sub-Committee noted that increases in disease-free survival generally, but not always, translate into increases in overall survival when longer-term follow up data matures, although the benefit is generally smaller than for disease-free survival. Members noted that with hormonal therapies such as tamoxifen, there are good data to support such extrapolation. Members considered, however, that no such strong evidence exists for monoclonal antibodies.

The Sub-Committee noted that there are not yet any rapidly-available predictors of response to trastuzumab other than HER2 status. Members noted the pre-clinical data investigating the use of upregulated c-myc and preserved PTEN status as predictors of response to trastuzumab by Nagata et al (Cancer Cell. 2004 Aug; 6(2): 117-27.) They also noted the results of a Canadian study, utilising these data in a cost-effectiveness model for trastuzumab (Ragaz and Spinelli, Abstract 2029; San Antonio Breast Cancer Meeting, Dec 2005), but that the results were premature at the moment. Members noted that in the future these may reduce the target population by more than half, and improve the cost-effectiveness significantly.

The Sub-Committee noted that 15-25% of breast cancers are HER2-positive, meaning that around 500 women are diagnosed with HER2-positive breast cancer every year, and that of this some 90-95% would likely seek treatment with trastuzumab. Members noted that it is likely that, if funded, existing patients who have previously completed chemotherapy may also seek treatment with trastuzumab – the Sub-Committee considered that the delay in finishing prior treatment and starting trastuzumab should be no more than six months.

The Sub-Committee noted that breast cancer is more prevalent in Maori and Pacific Island women, but that there are no data to indicate if there are higher rates of HER2-positivity in these populations.

Members noted that the resource burden of administration of trastuzumab would be significant, with 18 infusions of 90 minutes each, plus preparation time, per patient over a year.

Members noted that the additional resource burden of the cardiovascular monitoring requirements would also be significant. Patients would be required to undergo 3-4 additional echocardiograms, with more required if any reduction in LVEF were detected. The Sub-

Committee noted that this would have the effect of adding additional costs to cardiac departments.

The Sub-Committee noted that at present both infusion and echocardiogram services are working at, or near, capacity in DHB hospitals, and if trastuzumab were available for early breast cancer, then it may mean increased waiting times for existing cancer treatments and may adversely impact cardiac services.

The Sub-Committee considered that trastuzumab could be made available for the treatment of early breast cancer, and gave a low-to-medium priority to this recommendation.

The Sub-Committee considered that the relevant decision criteria in favour of the recommendation were (i) the health needs of all eligible people within New Zealand, (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things and (viii) the Government's priorities for health funding. Members noted the other decision criteria were either neutral or against a positive recommendation.

Members noted that the priority rating could increase to high if the price of trastuzumab were to fall significantly, although such recommendation would be with caution, due to the lack of long-term safety and efficacy data and an absence of a proven increase in overall survival. Members noted that \$30 million per year may be better spent in other areas of cancer control if such funding was available. One member noted that given the extent of the funding required, consideration may need to be given as to whether such funding would be better directed towards other (non-cancer) health services.

The Sub-Committee noted that if trastuzumab was to be funded for early breast cancer, then the proposed Special Authority criteria would need to be modified to prevent a second course following relapse post-primary treatment with trastuzumab. Members noted that at present there is no evidence to suggest whether or not a benefit exists with further trastuzumab treatment in relapsed patients whom have previously been treated with trastuzumab.

## **Record of the Cancer Treatments Subcommittee of the Pharmacology and Therapeutics Advisory Committee Meeting held on 26 and 27 October 2006:**

### **Trastuzumab (Herceptin) for HER2 positive early breast cancer**

The Sub-Committee reconsidered an application from Roche for the use of trastuzumab in early breast cancer. The Sub-Committee noted that this had been considered previously by CaTSOP at its 19 April 2006 meeting and by PTAC at its 16 February 2006, 25 May 2006 and 17 August 2006 meetings.

The Sub-Committee reviewed the following material

- Minutes of all relevant PTAC and CaTSOP meetings
- Two year median follow-up of the one year treatment arm of the HERA trial supplied in the format of a PowerPoint slide presentation from the American Society of Clinical Oncology (ASCO) 2006 conference
- A technology appraisal from the University of Sheffield School of Health and Related Research (SchHARR) commissioned by the National Institute of Clinical Excellence (NICE)
- A PHARMAC technology appraisal report 'TAR 75 Trastuzumab (Herceptin) in HER-2 positive primary breast cancer'
- "Adjuvant Docetaxel or Vinorelbine with or without trastuzumab for Breast Cancer", Heikki Joensuu et al. (N Engl J Med 354:8, February 23 2006), the "FinHer study".

- Roche Pharmaceuticals' response to the 17 August 2006 PTAC minutes regarding trastuzumab;

The Sub-Committee noted that at its 17 August 2006 meeting PTAC recommended that the application for the funding of trastuzumab as per the HERA protocol (12 months treatment) be declined and that the application be referred back to the Cancer Treatment Subcommittee of PTAC to consider the clinical appropriateness of any funding regimen consistent with the FinHer protocol (9 weeks treatment).

#### ***ASCO 2006 slide presentation for the HERA study***

The Sub-Committee noted that the two-year follow-up data supported published one-year follow-up data indicating a benefit in disease-free survival and relapse rates in favour of trastuzumab. The Sub-Committee noted that data indicated an improvement in overall survival in favour of trastuzumab.

However, the Sub-Committee considered that although interesting, the two-year data were of limited value in the absence of formal publication in a peer reviewed scientific journal.

The Sub-Committee noted that the study design of HERA allowed switching of patients from the observation arm to trastuzumab treatment after publication of the one year follow-up data, when this had shown a reduced recurrence rate. The Sub-Committee considered that due to this switching data regarding the long-term efficacy and safety profile of trastuzumab in this study would be significantly compromised.

#### ***PHARMAC technology assessment report and ScHARR report***

The Sub-Committee considered the PHARMAC technology assessment report, which included a cost utility analysis. The Sub-Committee considered that PHARMAC's cost utility analysis (CUA) was consistent with the CUA included in the ScHARR report, and that the PHARMAC technology assessment report raised similar concerns regarding the costs and benefits of trastuzumab. The Sub-Committee considered that, in certain areas, the conclusions of the ScHARR report were not consistent with the main body of the report.

The Sub-Committee considered that PHARMAC's CUA may have underestimated the costs relating to the treatment of metastatic breast cancer, and suggested that the model could be adjusted to take into account treatment with sequential therapies rather than a single chemotherapy regimen. The Sub-Committee considered PHARMAC's CUA to be otherwise sound, and that all important clinical factors were included in the analysis. The Sub-Committee also considered that the conclusions outlined in the technology assessment report were reasonable.

#### ***The FinHer study***

The Sub-Committee noted that the study design and the data from a sub-analysis (232 of 1,010 patients) of FinHer was of good quality, however, the Sub-Committee considered that it had more confidence in the data from the HERA study (and the US studies NSABP B-31 and NCCTG N9831 reported in Romond et al NEJM 2005) given the larger number of patients involved in those studies.

The Sub-Committee considered that data from the FinHer study were valid in terms of statistically significant improvement in disease-free survival and relapse rates in favour of trastuzumab. The Sub-Committee noted that there was no statistically significant improvement in overall survival in favour of trastuzumab over the three year period measured to date, but noted that this may be due to the relatively small number of patients.

The Sub-Committee considered that although the number of patients enrolled in the FinHer study was smaller than other key trastuzumab studies (e.g. HERA and the two trials published as the Romond pooled analysis), the data were similar and therefore supportive of the conclusion that trastuzumab has biological activity against HER2 positive early breast cancer when dosed for 9 weeks. The Sub-Committee also noted that there appeared to be

less cardiovascular toxicity in the FinHer study which may be an advantage of 9 weeks trastuzumab dosing, although this could also be due to the much smaller numbers of patients exposed to trastuzumab in the FinHer study.

### ***General Discussion***

The Sub-Committee considered that there was still uncertainty about the best way of administering trastuzumab in terms of optimal treatment duration, dose and schedule (sequential to, or concurrent with, chemotherapy) and minimising cardiovascular toxicity. The Sub-Committee considered that more clinical research was needed to answer these questions and that it would be ideal to do a comparative 12 months trastuzumab vs. 9 weeks trastuzumab study.

### ***Recommendations***

The Sub-Committee ***recommended*** that trastuzumab be listed on the Pharmaceutical Schedule for HER2 positive early breast cancer. The Sub-Committee further ***recommended*** that, in the absence of availability of funding for 12 months treatment, 9 weeks treatment would be reasonable and gave this recommendation a high priority. However, the Sub-Committee noted, and wished to emphasize, that this recommendation was strongly based on financial considerations since the Sub-Committee had more confidence in the validity of the 12 month treatment results.

The Sub-Committee considered that if 9 weeks treatment with trastuzumab was to be funded for early breast cancer, then the proposed Special Authority criteria would need to restrict use to the FinHer protocol treatment regimen (i.e. concurrent with docetaxel and FEC60), however, the committee considered that the dose of epirubicin should be increased to at least 75 mg/m<sup>2</sup>.

The Sub-Committee considered that the relevant decision criteria in favour of the recommendation were (i) *the health needs of all eligible people within New Zealand*, (ii) *The particular health needs of Maori and Pacific peoples* (iii) *the availability and suitability of existing medicines, therapeutic medical devices and related products and related things*, (iv) *The clinical benefits and risks of pharmaceuticals* and (viii) *the Government's priorities for health funding*.