

Appendix One: Relevant minutes of clinical advisory committees meetings since mid 2006

PTAC further considered trastuzumab in August 2006, and then the cancer treatments subcommittee of PTAC (CaTSop) considered the FinHer study in November 2006. Subsequently PTAC have discussed this relevant CaTSop minute. Relevant minutes to TAR 75b (updated CUA for nine weeks treatment regimen) are included below:

Pharmacology and Therapeutics Advisory Committee (PTAC) – 17 August 2006

Herceptin new data

PTAC has twice considered trastuzumab for the treatment of early HER-2 positive breast cancer at its meetings of February and May 2006. These minutes should be read in conjunction with the February and May 2006 minutes found at <http://www.pharmac.govt.nz/pdf/ptacmins.pdf>

The Committee reviewed further information in support of a submission from Roche Pharmaceuticals for the listing of trastuzumab (Herceptin) on the Pharmaceutical Schedule for the treatment of early HER-2 positive breast cancer.

The Committee reviewed the following material:

- Roche Pharmaceuticals' response to previous PTAC and CaTSop minutes regarding trastuzumab;
- A technology appraisal from the University of Sheffield School of Health and Related Research (SchARR) commissioned by the National Institute of Clinical Excellence (NICE);
- Two year median follow-up of the one year treatment arm of the HERA trial in the format of a PowerPoint slide presentation from the American Society of Clinical Oncology (ASCO) 2006 conference;
- "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".

Correspondence from Roche Pharmaceuticals

The Committee noted Roche New Zealand's willingness to assist PHARMAC in the provision of evidence to support the use of trastuzumab.

The Committee expressed disappointment that additional trial data is unlikely to be available in a peer reviewed, published format in the near future.

SchARR report

The Committee noted that the SchARR report was very comprehensive and raised similar concerns regarding the costs and benefits of trastuzumab that had been highlighted in PHARMAC's own cost utility analysis and previous PTAC minutes.

Members noted that the final recommendation of the SchARR report did not appear to correlate to specific findings of the report.

ASCO 2006 slide presentation for the HERA study

The Committee noted the limitations of clinical data presented as a PowerPoint slide presentation, which have not been subjected to external peer review for a reputable scientific journal. The Committee reiterated its view that it does not consider slide presentations alone to be adequate for the purpose of making important clinical recommendations.

The Committee noted that after a median follow-up of one year, as presented in Piccart-Gebhart et al (N Engl J Med. 2005 Oct 20; 353(16): 1659-72.), there was a reported absolute increase in two-year disease-free survival of 8.4% in the trastuzumab arm compared with control. The Committee noted that the slides

indicated that after a median follow-up of two years the absolute increase in disease-free survival at three years in the trastuzumab arm compared with control had been reduced to 6.3%.

The Committee noted that the slides indicated that after two years follow-up the absolute overall survival difference at three years from randomisation, as displayed, was 2.7% in the trastuzumab arm against control, and appeared to be statistically significant. Members noted that this translated into a number needed to treat (NNT) of 37 patients.

The Committee considered that in an adjuvant setting an ongoing treatment effect would be expected with efficacy differences becoming greater over time. The Committee considered, however, that the difference in the HERA treatment groups would have been anticipated to continue to diverge, rather than converge, which appears to be the case from the slide data presented. The Committee noted that 861 patients in the non-trastuzumab arm switched to trastuzumab after 12 months. Members noted that some of the convergence seen may have been due to the loss of patients from the observation arm, although there was insufficient data presented in the slides to clarify this.

Members noted that switching of patients from the observation arm to trastuzumab treatment meant that the validity of the long-term efficacy and safety profile of trastuzumab from the HERA trial may be significantly compromised. Members noted that although half of the patients in the observation arm who had not switched over by two years would be able to be measured in subsequent years, they would no longer necessarily be representative of all patients randomised to the observation arm. Members noted that this inconsistency would only be rectified by maintaining intention-to-treat analysis of the efficacy of trastuzumab beyond the one year.

The Committee noted that in data presented as 'censored', (data that excluded patients who had switched from control to trastuzumab), the denominators were not small enough to account for removal of all switched patients. The Committee concluded that this apparent inconsistency would likely be addressed in a formal peer-reviewed publication of this data and highlighted the difficulties of evaluating clinical data from a slide presentation.

The FinHer study

The Committee considered that the FinHer study cast doubt over the optimal duration and timing of trastuzumab treatment. The Committee noted that the cost utility of trastuzumab use as per the FinHer protocol (9 weeks treatment) was likely to be appreciably better than 12 months treatment.

The Committee considered that the number of patients treated in the FinHer study (232) was substantial compared to many other cancer treatment trials.

The Committee noted that although HERA was a far larger trial, the number of patients treated in FinHer was not insignificant, and therefore the data from FinHer was valuable.

The Committee considered that the trastuzumab regimen used in the FinHer study resulted in comparable health gains to the regimen used in the HERA trial (11.7% absolute reduction in disease recurrence at three years against no trastuzumab), but produced less cardiotoxicity and other side effects, and was associated with a significantly reduced pharmaceutical and service cost.

The Committee considered that funding of trastuzumab as per the FinHer protocol (9 weeks treatment) could be considered.

Recommendations

The Committee **recommended** that the application for the funding of trastuzumab as per the HERA protocol (12 months treatment) be declined due to the uncertainty surrounding long term clinical benefits and risks; the uncertainty over optimal duration of treatment; and the high budgetary impact associated with treatment.

The decision criteria relevant to PTAC's recommendation were: (i) The clinical benefits and risks of pharmaceuticals; (v) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget).

The Committee **recommended** 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).

Cancer Treatments Subcommittee of PTAC (CaTSop) – 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 (SchARR) 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/m².

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*

Pharmacology and Therapeutics Advisory Committee (PTAC) – 15 / 16 November 2006

PTAC noted and accepted the minutes of the Cancer Treatments Sub-Committee of PTAC (CaTSoP) meeting held on 26 / 27 October 2006, with the following comments:

PTAC was cognisant of the promising preliminary data for trastuzumab and the need for more effective treatment options in this patient population.

However, PTAC reiterated 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), minimising cardiovascular toxicity and long-term clinical outcomes.

PTAC noted CaTSOP's discussion and recommendations regarding trastuzumab. The Committee noted that PHARMAC's amended base-case cost-utility analysis resulted in an indicative cost/QALY of \$12,300-\$29,200 for 9 weeks trastuzumab treatment as equivalent to the FinHer trial regimen; however, the Committee noted that this did not include the additional cost of docetaxel that was used in FinHer. PTAC noted that the absolute disease-free survival for trastuzumab-treated patients in the FinHer trial was 89% at three years, whereas the published absolute disease free survival in the HERA trial was 86% (95% confidence interval 83%-89%) at a median duration of one year.

The Committee considered that more clinical research was needed and that a study comparing 12 months trastuzumab with 9 weeks trastuzumab should be performed.

The Committee noted CaTSOP's view that, in the absence of availability of funding for 12 months trastuzumab treatment, 9 weeks treatment would be reasonable. PTAC **recommended** that, subject to an acceptable cost/QALY, including the cost of docetaxel, 9 weeks treatment with trastuzumab should be funded and gave this recommendation a high priority.

The Committee considered that the relevant decision criteria in favour of this 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, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule and (viii) the Government's priorities for health funding.*

Pharmacology and Therapeutics Advisory Committee (PTAC) – 21 / 22 February 2007

Trastuzumab (Herceptin) for HER2 positive early breast cancer

The Committee considered further information in relation to the application from Roche for the use of trastuzumab in HER2 positive early breast cancer. The Committee noted that this had been considered previously by PTAC at its February, May, August and November 2006 meetings. These minutes should be read in conjunction with the previous minutes found at <http://www.pharmac.govt.nz/pdf/ptacmins.pdf>.

The Committee reviewed the following material

- 6 January 2007 Lancet publication of the two-year median follow-up of the one-year treatment arm of the HERA trial (Smith et al) and the accompanying editorial (Hind et al);
- Power point presentation 'Phase III Trial Comparing AC-T with AC-TH and with TCH in the Adjuvant Treatment of HER2 positive Early Breast Cancer Patients: Second Interim Efficacy Analysis' BCIRG006 Trial; Slamon et al, presented at the San Antonio Breast Cancer Symposium (SABCS) 14-17 December 2006;
- Poster presentation 'Adjuvant Trastuzumab: Long-Term Results of E2198' Sledge et al, SABCS December 2006;
- 'Trastuzumab in Early Stage Breast Cancer' Huybrechts M, Hulstaert F, Neyt M, Vrijens F, Ramaekers D. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2006. KCE reports 34C (D/2006/10.273/25)
- New Zealand, Australian and USA trastuzumab Datasheets

The Committee noted that at its November 2006 meeting it considered that more clinical research was needed and that a study comparing 12 months trastuzumab with 9 weeks trastuzumab should be performed.

The Committee further noted it recommended that, subject to an acceptable cost/QALY, including the cost of docetaxel, 9 weeks treatment with trastuzumab should be funded and gave this recommendation a high priority.

The Lancet article and editorial – 2-year median follow-up HERA data

The Committee noted that the two-year median follow-up data published in the Lancet in January 2007 confirmed the results presented at the American Society of Clinical Oncology (ASCO) 2006 conference that were considered by the Committee at its August 2006 meeting.

The Committee noted that data for patients treated with two years trastuzumab in the HERA trial is still to be reported.

The Committee noted that the hazard ratio (HR) for the two-year median follow-up was 0.64 (95% confidence interval 0.54-0.76), compared with the one-year median follow-up HR of 0.54 that had been considered by the Committee and used in PHARMAC's cost-utility analysis of trastuzumab. The Committee considered that these two-year follow-up data indicated a possible waning of treatment effect compared with the previous one-year follow-up data, and noted that the graphs in the Lancet paper indicated a possible convergence in disease-free survival between the sequential trastuzumab and standard treatment arms after the first six months' follow-up.

The Committee noted that 55 patients would need to be treated to prevent one death after two years' median follow-up ('number needed to treat' (NNT)), and that one of every 51 patients would suffer an adverse cardiac event over the same time period ('number needed to harm' (NNH)). The Committee noted that this NNH would reduce to one in 20 patients having any form of cardiac toxicity including non-symptomatic reductions in left ventricular ejection fractions (LVEF).

The 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. It was noted that 861 out of 1698 patients in the original observation treatment group had switched to trastuzumab. The Committee reiterated that due to this non-randomised switching the control group had been 'lost'; therefore, interpretation of future long-term efficacy and safety data for trastuzumab in this study would be significantly compromised.

BCIRG006 trial results

The committee reviewed 36-month median follow-up data from the Breast Cancer International Research Group (BCIRG) 006 study (as yet unpublished) as an interim analysis supplied in the form of MS PowerPoint slides of a presentation at SABCS in December 2006. The Committee noted that it had reviewed an interim analysis of 23-months median follow-up data during its May 2006 Meeting. The Committee 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 (AC-T); the second containing the same chemotherapy regimen plus one year of trastuzumab commenced concurrently with docetaxel (AC-TH); and the third comprising six cycles of docetaxel and carboplatin with one year of trastuzumab commenced concurrently with the chemotherapy (TCH).

The Committee noted that there was a significant improvement in both disease-free and overall survival in the trastuzumab treated patients in this study. The Committee considered that there appeared to be no clinical difference between the AC-TH (containing the anthracycline doxorubicin) treated patients compared with TCH (containing no anthracycline) treated patients, although the slide presentation did not present the results of a formal statistical comparison between the two arms. Members noted, however, that cardiac toxicity was lower in the TCH treatment group; therefore, it questioned the clinical benefit of anthracycline use in this study.

E2198 trial results

The Committee reviewed the 5-year follow-up results of study E2198 presented as a poster at SABCS in December 2006. This study compared short duration trastuzumab (10 weeks) given concurrently with paclitaxel prior to anthracycline treatment, with the same treatment plus an additional 52 weeks trastuzumab after completion of anthracycline treatment.

The Committee noted similar clinical outcomes in the short duration concurrent regimen compared with the extended (52 weeks) trastuzumab treatment. The Committee considered that although the study was not designed to test efficacy, and was not powered to determine equivalence, the results supported the efficacy of short duration concurrent trastuzumab therapy when administered before anthracycline containing

chemotherapy, as demonstrated in the FinHer study, and supported the rationale for the SOLD study which would compare long versus short durations of concurrent trastuzumab regimen.

New Zealand Datasheet, Australian Product Information and USA Prescribing Information

The Committee noted that a key issue around its recommendation for funding 9 weeks treatment with trastuzumab (concurrent with chemotherapy) is that this treatment regimen is not currently covered by the Medsafe-approved Datasheet in New Zealand which specifies that trastuzumab is to be administered following completion of adjuvant chemotherapy (i.e. sequential treatment).

The Committee noted that the USA Prescribing Information recommends that trastuzumab is administered for 12 months starting concurrently with paclitaxel and that the Australian Product Information allows for 12 months sequential, 12 months concurrent or 9 weeks concurrent treatment regimens to be used.

The Committee specifically noted that the Australian Product Information states that 'The optimal dosage regimen and treatment duration have not been defined. A favourable risk/benefit ratio has been demonstrated with the following regimens:

Three weekly regimen (HERA trial): Treatment with HERCEPTIN was commenced following surgery and completion of neoadjuvant or at least 4 cycles of adjuvant chemotherapy.

Weekly regimen (B31/N9831 trials): Treatment with HERCEPTIN was commenced following surgery and completion of 4 cycles (12 weeks) of doxorubicin and cyclophosphamide (AC) chemotherapy, then together with paclitaxel for 12 weeks, then as a single agent for a further 40 weeks.

Weekly regimen (FinHer trial): Treatment with HERCEPTIN was commenced following surgery and was given concurrently with docetaxel or vinorelbine for a total of 9 weeks.'

The Committee considered that the Australian Product Information was consistent with its view that there was still uncertainty about the best way of administering trastuzumab.

The Committee noted that trastuzumab currently has provisional consent in New Zealand and, therefore, there may be an opportunity for Medsafe to align the New Zealand datasheet with that in Australia. The Committee resolved to write to Medsafe to request that it initiate a review of the datasheet, given the Committee's concerns that the datasheet specified sequential 12 months trastuzumab treatment, which the Committee considered may be inappropriate (given that the two-year median follow-up data from HERA, alongside the results of Arm B of study N9831, raised significant doubts about the magnitude of efficacy of sequential 12 months trastuzumab, and that concurrent regimens may be, at least as, if not more efficacious than sequential).

Cost-Utility Analysis

The Committee received a verbal update from PHARMAC staff regarding the trastuzumab cost-utility analysis (CUA), which had been updated to indicate the cost-effectiveness of the nine-week concurrent treatment regimen (as per FinHer). The Committee noted that the updated analysis included the cost of docetaxel (Taxotere), and made the conservative assumption that the cardiotoxicity risks and costs would be the same as seen in the HERA trial (because FinHer may have been underpowered to detect these risks).

The Committee noted that the base-case results of the revised CUA were less than \$20,000/QALY under conservative scenarios for effectiveness. The Committee considered that the inputs for the revised CUA were sound and noted that the cost-effectiveness of nine-week concurrent treatment with trastuzumab was comparable to other pharmaceuticals funded by PHARMAC.

The Committee noted the Belgian Health Technology Assessment report and considered that the conclusions outlined in the report were reasonable and consistent with the Committee's views.

General Discussion

The Committee reiterated its view 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), minimising cardiovascular toxicity, and long-term clinical outcomes.

Specifically, the Committee considered that data from Arm B of study N9831 raised significant doubts about the efficacy of sequential 12 months trastuzumab. The Committee noted that it had requested in May 2006 that full data from the N9831 trial be provided by the supplier, but thus far this had not been provided. The Committee considered that there was now likely to be longer-term follow-up of outcomes (disease free survival and mortality) in this study, and that all the updated data from all three arms of the trial should be made available to the Committee.

The Committee reiterated its recommendation from its November 2006 meeting that 9 weeks treatment with trastuzumab (concurrent with chemotherapy and before anthracycline) should be funded and gave this recommendation a high priority.

The Committee considered that more clinical research was needed to determine if long duration concurrent treatment (52 weeks) is any better than short duration concurrent treatment (9 weeks) and reiterated that a comparative study should be performed. The Committee noted CaTSoP's advice from its October 2006 meeting that the proposed SOLD study was well designed and would answer some of the questions relating to the optimal dose, duration and scheduling of trastuzumab in early HER2 positive breast cancer.