

**Part (Item 9) of the Record of the
Pharmacology and Therapeutics Advisory Committee Meeting held on 21 & 22
February 2007**

9. Trastuzumab (Herceptin) for HER2 positive early breast cancer

9.1. 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>.

9.2. 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

9.3. 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

9.4. 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.

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

9.6. 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.

- 9.7. 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).
- 9.8. 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

- 9.9. 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).
- 9.10. 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

- 9.11. 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.
- 9.12. 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

- 9.13. 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).
- 9.14. 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.
- 9.15. 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.'
- 9.16. 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.
- 9.17. 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

- 9.18. 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).

- 9.19. 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.
- 9.20. 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

- 9.21. 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.
- 9.22. 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.
- 9.23. 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.
- 9.24. 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.