

Cancer Treatments Subcommittee (CaTSoP) meeting held 13 June 2008

Trastuzumab for HER 2 positive early breast cancer

1. The Subcommittee considered further information from Roche Products NZ Limited for the use of 12 months' trastuzumab in HER2-positive early breast cancer. Members reviewed the following information provided by Roche:
 - Abstract and slide presentation of the second interim analysis of the combined NCCTG N9831 and NSABP B-31 studies presented at ASCO 2007 (Perez E, et al. ASCO 2007. Abstract 512)
 - Abstract and slide presentation from the PACS04 trial presented at the 2007 San Antonio Breast Cancer Symposia (Speilmann M, et al. SABCS 2007. Abstract 72)
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withheld under section 9(2)(ba)(i) of the OIA
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2. The Subcommittee also considered summary graphs and tables provided by PHARMAC staff showing all the available disease free survival and overall survival data from relevant trastuzumab studies (HERA, NCCTG N9831, NSABP B-31, FinHer, BCIRG006 and PACS04) plotted against median follow-up time.
3. The Subcommittee noted that it had previously reviewed interim data reported from the combined NCCTG N9831 and NSABP B-31 studies (2 years median follow-up, Romond et al N Engl J Med. 2005 Oct 20; 353(16): 1673-84) and that the updated ASCO 2007 data demonstrated that efficacy had been maintained out to 2.9 years median follow-up.
4. The Subcommittee noted that it had not previously seen data from study PACS04, and this constituted new evidence. Members noted that this was a randomised, multicentre, phase III trial designed to evaluate the benefit of docetaxel/epirubicin versus anthracyclines (FEC100) in the adjuvant treatment of node-positive early breast cancer. HER2-positive patients were further randomised to receive, or not receive, 12 months trastuzumab commenced following chemotherapy treatment (i.e., sequential treatment). Members noted that of 528 HER2-positive patients, 260 were randomised to receive trastuzumab and 268 to observation. Members noted that after a median follow-up of 48 months (four years) there was no statistically significant difference in disease free survival or overall survival between the trastuzumab and observation treatment groups.

5. The Subcommittee noted that some parties had criticised the validity of data from the PACS04 study because approximately 10% of trastuzumab randomised patients did not start treatment and approximately 18% of patients did not complete the full 12 months of treatment. Members considered that these criticisms were invalid because the same situation applied to other trastuzumab studies, for example in the Romond study (combined NCCTG N9831 and NSABP B-31) approximately 10% of patients failed to commence treatment and an additional 20% of patients did not complete more than nine months of trastuzumab therapy. Members considered that despite the PACS04 study being smaller than some of the other 12 month trastuzumab studies the data were of good quality.
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withheld under section 9(2)(ba)(i) of the OIA

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7. The Subcommittee considered that the main body of evidence for trastuzumab in HER2-positive early breast cancer comprised four studies examining concurrent treatment (NCCTG N9831, NSABP B-31, BCIRG006 and FinHer) and three studies examining sequential treatment (HERA, NCCTG N9831 and PACS04). Members considered that evidence from the all concurrent studies was consistent with trastuzumab producing a relative risk reduction in disease recurrence of around 50% and around 33% in overall survival. The Subcommittee considered that results of the FinHer study supported a similar overall survival benefit; however, members noted that this benefit did not reach statistical significance, likely due to the small size of the FinHer study.
8. The Subcommittee noted that although data from the HERA study for sequential trastuzumab treatment were similar to the concurrent studies, both PACS04 and NCCTG N9831 (sequential arm) demonstrated non-statistically significant improvements in disease free survival for sequential trastuzumab treatment.
9. The Subcommittee considered that trastuzumab treatment was associated with an increased risk of cardiotoxicity. Members considered that evidence to date indicated that the early cardiotoxicity was generally manageable and reversible; however, less information was available regarding late-stage cardiac toxicity. Members commented that the assessment tools for cardiotoxicity used in the trials were crude, for example a patient has generally lost a considerable degree of heart function before it can be detected on an ECHO cardiogram and normal echocardiograms frequently occur in patients in heart failure (Ewer J, Lenihan D. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground (Editorial). *J Clin Oncol* 2008;26:1201-1203). Therefore, members considered that although diagnostic testing appeared to show reversibility of trastuzumab-associated cardiotoxicity, patients' hearts may not have returned to normal. Members noted that the longer-term risks of trastuzumab associated cardiotoxicity were still unknown.
10. The Subcommittee considered that the weight of evidence indicated that concurrent treatment with trastuzumab was probably more efficacious than

sequential treatment, although, with the exception of nine weeks treatment, concurrent treatment was associated with increased cardiotoxicity.

11. The Subcommittee considered that more clinical research was needed to determine the optimal duration of trastuzumab treatment, and reiterated its support for the SOLD study which is designed to compare 12 months' concurrent trastuzumab with nine weeks' concurrent trastuzumab.
12. The Subcommittee noted that the benefits of trastuzumab treatment in the HERA study had decreased over time, whereas the benefits in the combined data from NCCTG N9831 and NSABP B-31 were maintained. Members considered that it was too early to say if the early benefits seen for trastuzumab were durable long-term. The Subcommittee considered that further follow-up data from all studies were necessary to determine the durability of efficacy for trastuzumab treatment; however, members noted that longer-term data may be confounded by cross-over in some of the studies.
13. The Subcommittee noted that there was no additional information of relevance presented at the recent American Society of Clinical Oncology meeting (ASCO 2008).
14. The Subcommittee considered that the weight of evidence currently supported 12 months concurrent treatment; however, the cost of trastuzumab was very high and, therefore **recommended** that the current nine weeks funding of trastuzumab for HER2-positive early breast cancer remained reasonable.
15. The Subcommittee considered the decision criteria relevant to this recommendation are: *(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; (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) of any changes to the Pharmaceutical Schedule; and (viii) The Government's priorities for health funding.*