PTAC meeting held 4 July 2008

(minutes for web publishing)

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- enable PHARMAC to carry on, without prejudice or disadvantage, negotiations, including commercial negotiations (section 9(2)(j)).

Trastuzumab for HER2-positive early breast cancer – new data, and clinical advice for cost utility analysis

1. The Committee noted the High Court judgement CIV 2007-485-1386 that directed PHARMAC make a new decision on Roche Products NZ Ltd application for 12 months' funding for trastuzumab (Herceptin); and noted that PHARMAC had referred new information to the Committee for its assessment and advice.

2. The Committee 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)

   - [
     withheld under section 9(2)(ba)(i) of the OIA
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3. Members noted that this information had been reviewed by the Cancer Treatments Subcommittee of PTAC (CaTSoP) at its 13 June 2008 meeting.

4. Members also noted that the supplier had provided a Commercial in Confidence funding proposal for 12 months trastuzumab.

5. The Committee also considered a paper by PHARMAC staff seeking the Committee's advice on clinical issues relevant to further cost utility analysis (CUA) for 12 months adjuvant trastuzumab (sequential and concurrent regimens).

6. The Committee reiterated the limitations of clinical data presented as conference abstracts and PowerPoint slide presentations. Members noted that such data had not been subjected to external peer review for formal publication, and that conference abstracts and presentations had insufficient detail to allow adequate critical appraisal. The Committee reiterated its view that in general it does not consider slide presentations or abstracts alone to be adequate for the purpose of making important clinical recommendations.

7. However, the Committee considered that data for trastuzumab in HER2-positive early breast cancer had been, and continues to be, subject to publication bias. The Committee noted the non-publication to date of results that have been presented at major conferences (BCIRG006 all analyses, B31/N9831 concurrent 2.9 year follow-up, N9831 sequential arm, PACS04), the comparatively poor dissemination of negative results, and the non-reporting of potentially important data (e.g. from HERA 2-year trastuzumab arm). Therefore, the Committee felt compelled to consider all relevant data sources regardless of format or detail.

8. The Committee also considered summary graphs, tables and further analyses provided by PHARMAC staff covering the available disease-free survival and overall survival data from relevant trastuzumab studies (HERA, NCCTG N9831, NSABP B-31, FinHer, BCIRG006 and PACS04), and draft CaTSoP minutes from its 13 June 2008 meeting.

9. Finally, the Committee, at the request of PHARMAC staff, reviewed a submission from the New Zealand Association of Cancer Specialists, Breast Special Interest Group (NZACS-BSIG) received by PHARMAC in response to its recent consultation on a proposal to decline 12 months funding for trastuzumab.

In relation to the second interim analysis of the combined NCCTG N9831 and NSABP B-31

10. The Committee noted that the new information provided for the 12 months concurrent regimen was limited to the abstract and slide presentation results, and considered it was not of sufficient quality to draw substantive conclusions.

11. The Committee agreed with CaTSoP's view that the updated data indicated that efficacy had been maintained out to 2.9 years median follow-up. Members further noted that cardiotoxicity was also apparent with this regimen.

12. The Committee reiterated that data from Arm B of study N9831 (12 months sequential trastuzumab) was still unpublished despite a presentation at ASCO in 2005 that raised significant doubts about the efficacy of this regimen. 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 it has not been provided. The Committee considered that there was now likely to be longer-term follow-up of outcomes in this study, and that the updated data from all three arms of the N9831 trial should be published. Members reiterated that data from the two studies of the Romond publication, B31 and N9831, should be published separately.

In relation to PACS04

13. The Committee noted that it had not previously seen data from study PACS04, and this constituted potentially new evidence for the 12 months' sequential trastuzumab regimen. The Committee noted, however, that the information provided, was limited to the abstract and slide presentation results.

14. The Committee agreed with CaTSoP's view that sequential treatment in PACS04 after a median follow-up of 48 months (4 years) was not associated with a statistically significant difference in disease-free survival or overall survival between

the 12-month sequential trastuzumab and observation treatment groups. Members further agreed with CaTSoP's view that criticisms of the study were invalid. The Committee specifically noted that the study was adequately powered (80%) to detect a difference between treatment groups of 38%, and that the lack of a statistically significant result at four years may be due to more events occurring in the trastuzumab treatment arm than expected.

15. The Committee noted that PACS04 was the second study (in addition to N9831) to indicate no statistically significant benefit for 12 months' sequential trastuzumab over the observation treatment group, and that both these important results remain unpublished at this time.

In relation to the [

withheld under section 9(2)(ba)(i) of the OIA

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In relation to all relevant data

16. The Committee 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).

17. The Committee agreed with CaTSoP's view that trastuzumab treatment was associated with an increased risk of cardiotoxicity, especially in the concurrent setting. Members considered that evidence to date indicated that, at least in the medium term, trastuzumab-associated cardiotoxicity was generally manageable with cessation of trastuzumab and at times the initiation of other pharmaceutical treatment. Members considered that monitoring for cardiac function ideally should be conducted monthly over the duration of trastuzumab treatment (12 months or nine weeks); however in the studies, and most likely in clinical practice this would only be conducted once every three months. Members noted that some factors seemed to predict worse cardiac outcomes in patients treated with trastuzumab including older age and prior administration of anthracycline chemotherapy. Members considered that information was not available regarding the long-term effects of cardiotoxicity and the assessment tools used for assessing cardiotoxicity in the trials, i.e. decrease in left ventricular ejection fraction (LVEF), had poor sensitivity and therefore may not

pick up all clinically relevant harm. Members considered that although cardiotoxicity, at least in the medium term, appears to be reversible with withdrawal of trastuzumab treatment in the majority of patients, and any residual cardiac dysfunction is manageable, some patients could still have sustained sufficient cardiac damage to require long term treatment for cardiac dysfunction. Therefore, the long term outcomes for these patients, including premature death from heart failure is unknown. Members further considered that in clinical practice the rate of trastuzumab associated cardiotoxicity may be higher than that seen in the trials due to less frequent monitoring and the treatment of patients with poorer baseline cardiac function.

18. The Committee considered that the data regarding the cardiotoxicity of trastuzumab should be referred to the Cardiovascular Subcommittee of PTAC for review, in order to gain advice on: establishing baseline cardiac function prior to trastuzumab treatment; which patients should be excluded from treatment; the optimum monitoring technique and interval; appropriate stopping rules; the management of trastuzumab-associated cardiac toxicity; and comment regarding logistical issues for DHBs in providing monitoring and treatment services.

19. The Committee agreed with CaTSoP's view that although data from the HERA study for sequential trastuzumab treatment initially showed a similar treatment benefit to the concurrent studies, the improvements in disease-free survival for sequential trastuzumab treatment in both PACS04 and NCCTG N9831 (sequential arm) were smaller and were not statistically significant. Members reiterated the Committee's view that the HERA two-year follow-up data, published in the Lancet in 2007, suggested a waning of treatment effect compared with the previous one-year follow-up data.

20. The Committee reiterated its view that there was still uncertainty about the best way to administer trastuzumab in terms of optimal treatment sequence, duration, minimising cardiovascular toxicity, and long-term clinical outcomes. Members commented that the emerging data from studies seemed to indicate that 12 months sequential treatment with trastuzumab, per the Medsafe approved datasheet, may be a less effective use of the agent in treating HER2 positive breast cancer patients.

21. The Committee noted an analysis by PHARMAC staff of the disease-free survival and overall survival data from the four studies examining concurrent treatment (NCCTG N9831, NSABP B-31, BCIRG006 and FinHer). Members noted that efficacy of combined N9831/B31 had been maintained out to 2.9 years median follow-up; however, BCIRG006 arm AC-TH appeared to show a statistically-significant waning of efficacy over time within the trial results reported to date, with the hazard ratio for disease-free survival increasing from 0.49 at 23 months median follow-up to 0.61 at 36 months median follow-up ($p < 0.01$).

22. The Committee considered that, overall, the data reported to date for trastuzumab in HER2-positive early breast cancer demonstrated no statistically significant benefit of 12 months sequential trastuzumab in N9831 over 18 months median follow-up and PACS04 over four years median follow-up; an apparent waning of benefit with 12 months sequential trastuzumab in HERA over two years and 12 months concurrent trastuzumab in BCIRG 006 over three years; and maintained benefit for the 12 months concurrent trastuzumab in B31/N9831 combined over three years. Members

noted that FinHer, the trial of the nine weeks concurrent regimen, has yet to report further follow-up data beyond the 3-year median follow-up results.

In relation to the submission from ANZCS-BSIG

23. The Committee noted that two members of CaTSoP were members of ANZCS-BSIG, but it was not clear from the submission if all members had equal input to the document.

24. The Committee, having reviewed all the relevant data, specifically did not agree with the conclusion by ANZCS-BSIG that "*Trastuzumab given as adjuvant therapy for 12 months, particularly in an initial concurrent schedule, shows increasing benefits with time*". Members noted that, in their view, no trastuzumab studies had demonstrated increasing benefits over time in terms of reducing hazard ratios for disease progression events, only one study (combined B31/N9831) had shown maintained efficacy (no significant change in hazard ratios) with consequent continuing divergence in disease free survival (DFS) between treated and untreated groups, with all others showing either no statistically significant benefit (no significant differences in DFS), or relative efficacy waning over time (hazard ratios increasing with lessened divergence in DFS). Members also disagreed with the statement by ANZCS-BSIG that "*the curves for the published 12 months trastuzumab trials mirror the Oxford Overview curves strongly suggesting similar likely benefits from trastuzumab-based therapy, as a result of the biology of breast cancer*", as the statement did not consider the likely waning of effect seen in the published HERA and the unpublished BCIRG006 and PACS04 trials, and, furthermore, the maintained effect suggested by the joint B31/N9831 3-year median follow-up analysis had not been published. Members noted that this point was important for the assessment of cost effectiveness of trastuzumab given the lack of available long-term data.

25. The Committee noted ANZCS-BSIG's view that Nuclear Medicine MUGA scans were appropriate for cardiac monitoring of patients treated with trastuzumab. Members noted that MUGA scanning was more readily available than ECHO monitoring, but this was because most cardiologists favour ECHO over MUGA scanning due to better specificity and sensitivity. Members reiterated their previous comments about the inadequacy of measuring LVEF decline as a surrogate for heart damage.

26. The Committee noted the ANZCS-BSIG's criticisms of FinHer, including comments regarding imbalance in treatment groups, and that these had been answered by PHARMAC staff last August in response to similar criticisms raised by Dr Richard Isaacs and others in the New Zealand Medical Journal (Metcalfe S, Evans J. PHARMAC responds on Herceptin assumptions and decisions. N Z Med J 2007;120:U2692).

27. The Committee recommended that PHARMAC staff reply to the ANZCS-BSIG outlining the Committee's view in relation to the points raised in their submission and discussed above.

In relation to clinical issues relevant to further cost-utility analysis

28. The Committee agreed that it was appropriate for the disease progression of patients with HER2-positive disease not treated with trastuzumab to result in baseline overall

survival curves consistent with recently published 10-year follow-up registry and adjuvant chemotherapy trial data (FinProg data http://www.finprog.org/ HER2-positive vs. HER2-negative; Pritchard et al. N Engl J Med 2006;354:2103-11). Members noted that the FinProg registry and the trastuzumab trial data to date indicated an improved prognosis for HER2-positive patients than as had been assumed in previous PHARMAC cost utility analyses (CUAs).

29. The Committee agreed that it was appropriate to update the trastuzumab clinical trial-derived specific relative risks to model the benefit of treatment (i.e. the effect of trastuzumab on disease progression) in the CUA model. Members considered it appropriate for the base case analyses to use the central estimates of effect for disease progression derived from the available hazard ratios (HRs). The Committee agreed that component data comprising the pooled reported results from the HERA 23-month median follow-up, N9831 sequential arm and PACS04 trials should be used to derive an overall HR for 12-months sequential treatment (fixed effects model); the pooled reported results of the 2.9 year median follow-up of the N9831 concurrent arm and B31 trials and the 3-year median follow-up of the BCIRG006 AC-TH arm to derive an overall HR for 12-months concurrent treatment (fixed effects model); and the reported FinHer 3-year median follow-up results be used for nine weeks concurrent treatment.

30. Given there are no other data and notwithstanding the smaller number of treated patients in the FinHer trial, the Committee agreed that it was appropriate for base case analyses to model the comparative efficacy of the 12 months sequential, 12 months concurrent and nine weeks concurrent regimens from overall pooled hazard ratios for disease events of 0.72, 0.53 and 0.42 respectively.

31. The Committee also agreed that it was appropriate to undertake sensitivity analyses that modelled 'worst case' probabilities for disease progression, derived from the upper 95% confidence interval limits for the HRs as reported, to mitigate differential biases from the greater imprecision with the nine week concurrent regimen. Members therefore agreed it appropriate to model the comparative efficacy of the 'worst case' results between 12 months sequential, 12 months concurrent and nine weeks concurrent regimens from the upper 95% confidence limits for the overall HRs for disease progression of 0.78, 0.60 and 0.83 respectively.

32. In considering the above probabilities for use in the CUA models, the Committee highlighted again that much of the relevant trial data remains unpublished (N9831 sequential arm, PACS04, B31/N9831 concurrent arm 2.9-year median follow-up, BCIRG006 arm AC-TH), and hence it was difficult to assess the quality of the overall probabilities used for the 12 months sequential and 12 months concurrent models.

33. The Committee considered it appropriate to assume a three-year period of benefit from adjuvant trastuzumab when modelling the durability of response. The Committee considered that three years duration was the extent to which there was reliable published evidence from the clinical trial data reported to date. The Committee did not consider that modelling a five-year period benefit was appropriate (as modelled in the UK ScHARR report).

34. The Committee considered that some waning of treatment benefit should be included in the base case scenario of the updated CUA model, and that assumptions of either

no waning of effect or different rates of waning should be modelled in sensitivity analyses.

35. The Committee considered that, on the balance of probability, it was most realistic to assume in the base case that the benefit of trastuzumab is not long-lasting but that some benefit would remain in the medium term. Members noted that this meant a proportion of patients treated with trastuzumab would have a lower risk of disease recurrence that continued beyond the period of benefit, but that trastuzumab-treated patients would eventually adopt the baseline risk of disease recurrence, with no further treatment benefit.

36. Conversely, the Committee did not consider other options presented for waning of treatment effect to be as appropriate, including scenarios that resulted in rapid convergence or non-divergence in DFS curves following the period of benefit. Of note, the Committee did not consider a lifetime benefit scenario to be appropriate, where the benefits seen in the trials over the first three years are maintained indefinitely for the rest of patients' lives, so that disease-free survival curves continue to diverge.

37. The Committee considered that the different rates of cardiotoxicity with the different regimens are clinically important and should be included in the updated cost-utility analyses. The Committee considered that in clinical practice there may be higher rates of cardiotoxicity than those reported in the clinical trials, due to less stringent cardiac exclusion criteria and monitoring being applied to patients in clinical practice compared with those applied in the clinical trials, and that this should be considered in the CUA. The Committee considered that it would be acceptable at this stage, for the specific purposes of CUA modelling, to assume that the majority of the cardiac side effects were manageable on cessation of trastuzumab treatment with some cases requiring ongoing other long term treatment. The Committee considered at this stage it would not be unreasonable for the updated CUA to assume no appreciable long term clinical consequences from trastuzumab-associated cardiotoxicity.

General Discussion and Recommendations

38. The Committee reiterated its view that there was still uncertainty about the best way of administering trastuzumab in terms of optimal treatment sequencing, duration, minimising cardiovascular toxicity, and long-term clinical outcomes.

39. The Committee considered that no new information had been presented that demonstrated any additional health benefit for 12 months trastuzumab (sequential or concurrent) over the currently funded nine-week concurrent regimen.

40. The Committee **recommended** that, given the questions around the efficacy of 12 months sequential trastuzumab, its high cost and associated cardiotoxicity, the application for funding this regimen should be declined.

41. The Committee considered that, although the weight of evidence supports the use of 12 months concurrent trastuzumab, when taking into account the Committee's concerns regarding this regimen's durability of efficacy, increased cardiotoxicity, its high cost and the lack of conclusive evidence of additional health gain over the

currently funded nine-week regimen, the Committee on balance **recommended** that funding for the 12 months concurrent regimen should be declined at this time.

42. The Committee **recommended** that current funding for nine weeks treatment with trastuzumab (concurrent with chemotherapy and before anthracycline) be continued.

43. The Committee reiterated its view that more clinical research was needed to determine if longer duration concurrent treatment (12 months) is any better than short duration concurrent treatment (9 weeks) and noted that the SOLD study was being performed to answer this question.

44. Finally, the Committee again reiterated its view that trastuzumab data in HER2-positive early breast cancer was subject to unacceptable publication bias. Members considered that data from arm B of N9831 (sequential 12 months trastuzumab), individual results from N9831 and B31 and data from the two year arm of HERA should have been published, and their continued absence raised questions as detailed in the Lancet May 2008 publication (Metcalfe et al. Lancet 2008;371:1646-8.).

45. The Committee considered the decision criteria relevant to these recommendations 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; (iv) 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) of any changes to the Pharmaceutical Schedule and (viii) The Government's priorities for health funding.*