

**Part (Item 20) of the Record of the
Pharmacology and Therapeutics Advisory Committee Meeting
held on 15 & 16 February 2006**

(paragraph 20.19 as amended by PTAC in May 2006)

20 Trastuzumab (Herceptin)

- 20.1 The Committee considered an application from Roche relating to the use of trastuzumab (Herceptin) for early breast cancer. The Committee noted that trastuzumab has not been registered for use in early breast cancer, although Roche had submitted an application to Medsafe. Members further noted that trastuzumab had not yet been licensed for this indication in any other country. The Committee noted that it was unusual for PTAC to consider applications for unregistered medicines or for unregistered indications of registered medicines. However, PTAC noted the high level of public concern and considered that they could give a preliminary view.
- 20.2 The Committee noted that the application was for adjunctive treatment of HER2-positive early breast cancer for patients who have previously undergone surgery and a course of chemotherapy. Members noted that trastuzumab is currently registered and funded for the treatment of metastatic disease.
- 20.3 The Committee noted that patients with HER2-positive breast cancer (around 20%) have a poorer prognosis than for patients with other breast cancers, with an average survival of approximately 50% after ten years.
- 20.4 The Committee noted that the submission focused primarily on two studies published recently in the New England Journal of Medicine, the first by Piccart-Gebhart et al – reporting interim results of the HERA trial, and the second by Romond et al – reporting a pooled analysis of data from study B-31 and partial results of study N9831. The Committee noted that all studies were open label.

Piccart-Gebhart et al (HERA trial)

- 20.5 Members considered the paper by Piccart-Gebhart et al (N Engl J Med. 2005 Oct 20; 353(16): 1659-72.), an interim analysis after 1 year of a planned 2-year study. Members noted that this was an unblinded study.
- 20.6 The Committee noted that the HERA trial was divided into three treatment arms:
- Arm 1: trastuzumab for one year (1694 patients)
 - Arm 2: trastuzumab for two years (1694 patients)
 - Arm 3: observation (1693 patients)
- 20.7 Members noted that the HERA trial results were analysed early, and that the paper reported only the results from arm 1 and arm 3. The Committee considered that the interim results from the second arm should also have been available to the authors, but noted that they were not included in the analysis.
- 20.8 The Committee noted that the primary measure in the HERA trial was disease-free survival; secondary measures included cardiac safety, overall survival, site of first disease-free survival event and time to distant recurrence.

- 20.9 The Committee noted that for patients followed up to two years (16% of enrolled patients) there was an 8.4% absolute increase in disease-free survival in the trastuzumab arm although there was, as expected, no significant increase in overall survival. Members further noted that 98% of patients enrolled in the study were alive at two years.
- 20.10 Members noted that there were fewer distant metastases in patients treated with trastuzumab, although there appeared to be an increased incidence of central nervous system metastases in patients treated with trastuzumab. Approximately one quarter of women in the trastuzumab arm who developed distant disease had central nervous system metastases.
- 20.11 The Committee noted that there was an increase in heart failure with trastuzumab and that at two years, 0.5% of patients in the treatment arm had developed moderate to severe (NYHA grade III or IV) heart failure (0% in placebo group). 7.1% experienced a decrease in left ventricular ejection fraction (LVEF) compared with 2.2% in the observation arm. Members noted that, in addition, 143 patients (8.5%) withdrew from the trastuzumab arm, most withdrawals appeared to follow adverse events. Members considered that it was not clear from the report whether these patients were included in the reported heart failure events.
- 20.12 The Committee noted that in the study, patients had their cardiac function assessed immediately following chemotherapy, and patients were excluded from commencing therapy with trastuzumab if their LVEF was less than 55%. Members noted that in New Zealand, patients could typically wait up to six months for an echocardiogram. This could mean that, if patients were to begin treatment with trastuzumab immediately following chemotherapy, they could possibly be doing so without having their cardiac function assessed. Members considered that this was an issue that would need to be addressed, should DHBs decide to fund trastuzumab for early breast cancer.
- 20.13 Members noted that they would like to review the 1-year data from the 2-year trastuzumab arm, and the longer-term data of the other arms when available.

Romond et al

- 20.14 Members considered the paper by Romond et al (N Engl J Med. 2005 Oct 20; 353(16): 1673-84.), pooled results of study B-31 and some of the results of N9831. Members noted that these studies were divided into the following treatment arms:

B-31

Arm 1: 12 weeks of paclitaxel

Arm 2: 12 weeks of paclitaxel plus trastuzumab for one year (started at same time)

N9831

Group A: 12 weeks of paclitaxel

Group B: 12 weeks of paclitaxel then trastuzumab for one year

Group C: 12 weeks of paclitaxel plus trastuzumab for one year (started at the same time)

- 20.15 The Committee noted that the results of each trial had not been published separately, and considered that, rather than a pooled analysis being published, each trial should have been published individually, with a subsequent meta-analysis (not a pooled analysis). Members noted that there were some significant differences between the

papers that make comparison difficult, such as the timing of paclitaxel and the use of hormonal and radiation therapies. Members also noted that both trials were unblinded.

- 20.16 The Committee noted that the results of Group B of study N9831 were not included in the report, and that this was the only arm in the two studies that was of direct relevance to the application. Members considered that the efficacy results of this paper are of limited value.
- 20.17 The Committee noted that at median follow-up (2 years) there was a 9.6% absolute increase in disease-free survival in the trastuzumab arm, an 11.7% increase by three years, and by 4 years of follow-up an 18.2% increase. Members noted, however, that the 4-year follow-up data were based on relatively few patients; 165 patients (5% of the 3351 enrolled in the studies) had data out to 4 years, with 133 alive at that time.
- 20.18 The Committee considered that while it was possible that disease-free survival could translate into overall survival in the long-term, there was insufficient evidence upon which to extrapolate this benefit reliably. However, the Committee noted that there were 62 deaths in the trastuzumab arm and 92 in the control arm of the report, with an overall survival increase of 2.5% at three years, and 4.8% at four years.
- 20.19 The Committee noted that adverse cardiac events for each trial were reported separately. In trial B-31 there was an increased rate of severe (NYHA III or IV) heart failure or death at 3 years, of 4.1% in the trastuzumab arm versus 0.8% in the observation arm. In trial N9831, the rate of severe (NYHA III or IV) heart failure or death was 2.9 % in the trastuzumab arm versus 0% in the observational arm. The Committee noted further that the pooled rate of discontinuation in this paper was even higher than in the HERA trial, with 364 (31.4%) patients having discontinued treatment with trastuzumab in the first year, 164 (14.2%) due to asymptomatic decreases in LVEF and 54 (4.7%) due to symptoms of cardiac failure or other adverse cardiac effect). Members also noted that patients taking trastuzumab appeared to have an increase in adverse respiratory side-effects, with four patients in trial B-31 developing interstitial pneumonitis, one of whom died.

General

- 20.20 The Committee considered that the long-term cardiac safety of trastuzumab is unclear, and that there is insufficient evidence to indicate whether the risks are dose-related, or if they are reversible upon cessation of treatment.
- 20.21 The Committee considered that both the benefit and safety data for trastuzumab in early breast cancer were premature at present.
- 20.22 The Committee noted that the increased risk of heart failure would also be present when used in metastatic disease, but that in this situation the risk/benefit ratio is considered to be acceptable. Members noted that with early disease around 50% of patients are still alive after 10 years, whereas with metastatic disease none would be alive at this time – therefore consideration of the long-term risk of severe heart failure is more important when treating early disease than in metastatic disease. The Committee considered that in the case of early disease, the addition of trastuzumab could put at risk patients who would otherwise have survived.

- 20.23 The Committee considered that if trastuzumab was to be used for early breast cancer, then that patient's cardiac status would need to be monitored throughout treatment, and that there would be resultant increases in non-pharmaceutical expenditure.
- 20.24 The Committee noted that discontinuation rates for those undergoing trastuzumab in the trials were reasonably high, and that this was despite strict exclusion criteria and high levels of monitoring.
- 20.25 The Committee noted that the projected \$30 million cost per year was based on one year of treatment per patient, but noted that the trial data for two years would be available soon, and might indicate that there was a significant benefit in longer treatment. If this was the case the cost would be in the nature of \$60 million per year.
- 20.26 One member noted that there may be other priorities for breast cancer control that may confer greater population health gains than by funding trastuzumab to the above extent. These might include improved access to services and earlier presentation, diagnosis and follow up in order to reduce the numbers of patients presenting with more advanced breast disease.
- 20.27 The Committee considered that it could not recommend listing at this time. Members considered that before making a recommendation, the Committee should wait until trastuzumab received approval from Medsafe for use in early disease.
- 20.28 The Committee **recommended** that in the meantime, to maintain progress with the application for funding, PHARMAC staff should request that Roche supply the individual results of the trials B-31 and N9831, a meta-analysis (not pooled) of those two trials, and details of complete follow-up of all patients in all three studies considered to date, including all-cause mortality.
- 20.29 The Committee **recommended** referring the application to CaTSoP once these have occurred. The CaTSoP recommendation will then be taken to PTAC for a final listing recommendation.