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FOR CONSIDERATION BY PTAC FEBRUARY 2017

Dear Danae,

The NZ Breast Cancer Foundation and Breast Cancer Aotearoa Coalition (BCAC) would like to again endorse PHARMAC's decision to fund pertuzumab for patients with HER2+ metastatic breast cancer. We are grateful to the PTAC and its subcommittee specifically, for its consideration of the evidence in this matter and its recommendations for funding.

However, we were disappointed that patients currently receiving trastuzumab for metastatic breast cancer were excluded from accessing pertuzumab.

Our understanding is that up to 160 New Zealand women are currently being treated with trastuzumab for metastatic breast cancer (this number was supplied by Roche NZ in November 2016). This treatment regimen falls short of best practice defined in the ABC2 guidelines (consensus from the ABC2 conference, Lisbon, December 2013), which specify pertuzumab with trastuzumab and chemotherapy as the overwhelmingly preferred treatment for metastatic HER2-positive breast cancer.

Adding pertuzumab to traztuzumab has been scientifically proven to provide a more comprehensive signalling blockade in HER2 positive breast cancer. There is some clinical evidence that the combination is effective in patients who have already commenced on trastuzumab.

In a Phase II study, reported by Baselga et al. (2010), 66 patients who had previously been treated with trastuzumab for HER2-positive MBC and had disease progression received the combination of pertuzumab and trastuzumab every 3 weeks until further disease progression. All 66 patients were assessable for efficacy and safety. The objective response rate was 24.2%, and the clinical benefit rate was 50%. Five patients (7.6%) experienced a complete response, 11 patients (16.7%) experienced a partial response, and 17 patients (25.8%) experienced stable disease of > 6 months. Median progression-free survival was 5.5 months. Overall, the combination of pertuzumab and trastuzumab was well tolerated, and adverse events were mild to moderate. Cardiac dysfunction was minimal, and no patients withdrew as a result of cardiac-related adverse events (1).

A subsequent study showed that it was the combination of trastuzumab and pertuzumab rather than pertuzumab alone that was responsible for the activity (2).

There was a small crossover group from the CLEOPATRA trial who were initially randomised to the control group (n=48). These patients were still receiving the placebo combination, and had not progressed when OS improvement was reported (3), and were invited to cross over to pertuzumab. We have not been able to obtain results for this group from Roche. However, the publication by Swain et al. (2015) shows results for the analysis with this group included, censored and excluded from the analysis. The hazard ratios for survival and median survival gain in months were as follows:

Comparison	**N**	**HR for OS**	**Survival Pertuzumab**	**Survival Control**	**Median Survival Gain**
ITT population	808 (pert=402, control=406)	0.68 (0.56-0.84)	56.5 months	40.8 months	15.7 months
Crossover censored*	808 (pert=402, control=406)	0.63 (0.52-0.78)	56.5 months	39.6 months	16.9 months
Crossover excluded	760 (pert=402, control=358)	0.55 (0.45-0.67)	56.5 months	34.7 months	21.8 months

*data censored at the time of 1st pertuzumab dose

These results indicate that the results for the control group were improved because of the crossover group, indicating that the inclusion of these patients served to improve the overall outcome in the control group from 34.7 months to 40.8 months (4). The number of patients who opted to cross over was 48 (11.8% of the total control group population).

MEDSAFE granted consent for pertuzumab on 18 July 2013. An application for funding was first made to PHARMAC in November 2013. It has therefore taken PHARMAC and the supplier more than three years from the first application for funding to reach agreement to enable listing of pertuzumab on the Pharmaceutical Schedule. In the intervening period, women with metastatic breast cancer have commenced on other treatment for metastatic disease including trastuzumab (which is funded for this indication). That they should now be denied access to effective treatment because they have commenced on part of that regimen seems both contradictory and cruel.

Pertuzumab is now the international standard of care; there will therefore never be a robust clinical trial of pertuzumab for this small patient group, and thus the scientific evidence will never incontrovertibly support our stance (unproven benefit is of course quite different from saying there is insufficient actual clinical benefit). Many trastuzumab patients in Australia were offered pertuzumab under a grandfathering clause in the PBS listing. Failure to offer the same opportunity to NZ patients currently being treated with trastuzumab for metastatic breast cancer is a failure to offer them the best publicly funded treatment in NZ; we see no reason why these patients should continue to receive sub-standard treatment now that pertuzumab is funded.

In addition, we would like PHARMAC to reconsider its decision for three important reasons:

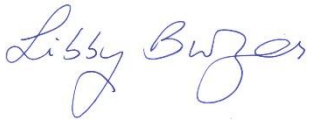
1. Several respected NZ oncologists concur with our stance, as indicated in the letter sent by the Breast Special Interest Group (representing the views of dozens of clinicians), which requested that PHARMAC consider funding all patients with metastatic Her2+ disease who are currently on trastuzumab alone, with or without chemotherapy, for delayed pertuzumab. (We acknowledge that individual SIG members offered varying opinions, and not all members commented).

2. In assessing the financial burden of expanding the patient group, there is a strong likelihood that only a small group of the 160 women currently taking trastuzumab would end up being treated with pertuzumab; that it would be taken up only by those patients most likely to benefit. In the CLEOPATRA trial, only 48 of the 406 patients in the intention-to-treat population of the placebo arm opted to cross over to the pertuzumab arm (NB, these patients had all been receiving trastuzumab for two years or longer).

3. There is a strong risk of further disadvantaging this patient group by unintentionally excluding them from future clinical trials, which are likely to include progression on trastuzumab AND pertuzumab in their eligibility criteria. This is a patient group for whom a clinical trial may well be the last hope of prolonged survival.

For these reasons, we strongly urge PHARMAC to extend funded pertuzumab to all patients currently being treated with trastuzumab for metastatic breast cancer.

Yours sincerely



Evangelia Henderson
Chief Executive
The NZ Breast Cancer Foundation

Libby Burgess
Chair
BCAC

1. Baselga J, Gelmon KA, Verma S, Wardley A, Conte P, Miles D, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(7):1138-44.
2. Cortes J, Fumoleau P, Bianchi GV, Petrella TM, Gelmon K, Pivot X, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(14):1594-600.
3. Swain SM, Kim S-B, Cortés J, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. The Lancet Oncology. 2013;14(6):461-71.
4. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. The New England journal of medicine. 2015;372(8):724-34.