Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

MEDICINES RECOMMENDED FOR NON-INCLUSION IN THE PHILIPPINE NATIONAL FORMULARY (PNF)

After thorough and careful deliberation, the Health Technology Assessment Council (HTAC) hereby makes public the **preliminary recommendation for the non-inclusion of pertuzumab for human epidermal growth factor receptor 2 (HER2)-positive breast cancer** in the Philippine National Formulary (PNF)**.**

This preliminary recommendation was based on the review and recommendation World Health Organization (WHO) on pertuzumab for early-stage (as adjuvant of neoadjuvant treatment) and metastatic stage breast cancer considering that the WHO evidence review matches the population, intervention, comparator, and outcomes (PICO) of the clinical research questions of the HTAC.

The evidence considered and excerpt of the WHO review and recommendation on pertuzumab is shown in the annex of this advisory.

All comments, inputs and/or appeals may be submitted until **04 February 2022** for consideration of the HTAC through email at hta@doh.gov.ph.

Should you wish to submit hard copies of your submissions, you may drop them off at the 4th floor, Philippine Blood Disease and Transfusion Center, Lung Center Compound, Quezon Avenue, Quezon Avenue, Quezon City. Appeals shall no longer be entertained after the prescribed deadline.

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Annex A. WHO evidence on the efficacy and safety of pertuzumab for the treatment of locally advanced, inflammatory, early-stage, and metastatic breast cancer

Note: The evidence presented below are lifted from the Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children)

Neoadjuvant treatment of locally advanced, inflammatory, or early-stage breast cancer

Efficacy results for the primary endpoint of the Phase II Neopsphere study (9 March 2012 clinical cut-off date) showed a statistically significant and clinically meaningful improvement in breast pathologic complete response (bpCR) rate in patients receiving pertuzumab plus trastuzumab plus docetaxel (Ptz + T + D) compared with patients receiving trastuzumab plus docetaxel (T + D) as neoadjuvant therapy (45.8% vs 29.0%).

A consistent pattern of results was observed regardless of pathological complete response (pCR) definition, with a higher pCR (ypT0/is N0) rate also reported in patients receiving Ptz + T + D compared with T + D (39.3% vs 21.5%). bpCR rates were lower in the subgroup of patients with hormone receptor-positive disease (ranging from 5.9% to 26.0% among the four arms) than in the sub-group with hormone receptor-negative disease (ranging from 27.3% to 63.2%), but the difference in pCR still favored Pertuzumab (Ptz) + Trastuzumab (T) + Docetaxel (D) compared with T + D.

*Point estimates of Progression-Free Survival (PFS) (defined as the time from the date of randomization to the first documentation of progressive disease or death) and Disease-Free Survival (DFS) from the five-year analysis were consistent with the benefit shown from the addition of pertuzumab to trastuzumab plus docetaxel in the primary analysis of pCR (regardless of the definition of pCR used) but **confidence intervals were wide and included the null value.** Hazard ratios for **PFS and DFS were 0.69 (95%CI 0.34 to 1.40) and 0.60 (95%CI 0.28 to 1.27)**, respectively, indicating a lower risk of PFS and DFS events in the Ptz + T + D arm compared with the T + D arm.*

In addition, results of the Phase II TRYPHAENA study show that long-term analyses of DFS and OS were conducted when median follow-up exceeded 60 months in all trial arms. DFS at 3 years was 87% (95%CI 79 to 95) in patients treated with Ptz + T + FEC/Ptz + T + D, 88% (95%CI 80 to 96) in patients treated with 5-fluorouracil, epirubicin, cyclophosphamide (FEC)/Ptz + T + D, and 90% (95%CI 82 to 97) in patients treated with Cyclophosphamide + Ptz + T + D (3-year DFS was 89% (95%CI 81 to 96) in the first group, 89% (95%CI 81 to 96) in the second group and 87% (95%CI 80 to 95) in the third group). Three-year OS followed a similar pattern: 94% (95%CI 89 to100) in the first group, 94% (95%CI 89 to 100) in the second group and 93% (95%CI 87 to 99) in the third group.

Adjuvant Treatment of early breast cancer with a high risk of recurrence

The results of the Phase III APHINITY study show that *estimates of IDFS event-free rates were 94.1% vs 93.2% at three years and 92.3% vs 90.6% at four years in the pertuzumab and comparator arms, respectively. The addition of pertuzumab to trastuzumab and chemotherapy reduced the rate of distant recurrences as first site of recurrence (4.7% vs 5.8%) and at any time in the study 5.0% vs 6.0%).*

Interim OS results numerically favored patients in the pertuzumab arm, but with only 26% of the events required for the final planned OS analysis, the data were immature at the primary data cut-off. There was ***no significant treatment effect with regard to mortality between treatment arms at this first interim overall survival analysis (HR 0.89, 95%CI 0.66 to 1.21).***

Improved IDFS was observed irrespective of the hormone receptor status, but the benefit of adding pertuzumab to trastuzumab and chemotherapy was more marked in patients with hormone receptor-negative disease ***(HR 0.76, 95% CI 0.56 to 1.04)*** *than for patients with hormone receptor-positive disease* ***(HR 0.86, 95% CI 0.66 to 1.13)****, indicating a 24% and 14% reduction in the risk of recurrence or death, respectively.*

Metastatic or locally recurrent, unresectable breast cancer

The Phase IIII CLEOPATRA study found a statistically significant and clinically relevant improvement in IRF-assessed PFS in the pertuzumab arm compared with the placebo arm (HR 0.62, 95%CI 0.51 to 0.75; p<0.001), with an increase of 6.1 months in median PFS (12.4 months in the placebo arm vs 18.5 months in the pertuzumab arm). The advantage in PFS appeared soon after the treatment is started (9 weeks), and was maintained from this point onwards. Benefit was observed in all pre-specified sub-groups tested.

At the data cut-off date for final OS analysis (February 2014) the results demonstrated a statistically significant improvement in survival with Ptz + T + D compared with Pla + T + D. Median OS was prolonged in the Ptz + T + D arm compared with the Pla + T + D arm (56.5 months vs 40.8 months; HR 0.68, 95%CI 0.56 to 0.84, p<0.001) (19). Sensitivity analyses defined to explore the impact of crossover on the OS result confirmed the robustness of the results in the intention-to-treat (ITT) population. Sub-group analyses of the final OS were consistent with the analysis in the whole ITT population and confirmed results from previous analyses.

Annex B. Excerpt of WHO recommendation on the non-inclusion of pertuzumab in the Essential Medicines List (EML)

The Committee acknowledged that pertuzumab was associated with a relevant survival benefit, well beyond the established threshold, as first-line treatment of metastatic breast cancer, based on the results reported in the CLEOPATRA trial. However, the Committee expressed ***reservations about the generalizability of CLEOPATRA results in metastatic breast cancer and consistency of the clinical effectiveness of pertuzumab*** *among studies both in early and metastatic breast cancer. These reservations are expanded below.*

The Committee noted that only approximately 10% of patients in CLEOPATRA had received trastuzumab in the adjuvant or neoadjuvant setting. ***The Committee was concerned that the observed survival gains may not therefore be generalizable to patients with metastatic disease who have received prior adjuvant or neoadjuvant trastuzumab, making the magnitude of benefit in this population sub-group uncertain.*** *The Committee also noted the results reported in the MARIANNE trial, where pertuzumab in combination with trastuzumab was not shown to have greater clinical benefit compared to trastuzumab plus chemotherapy or trastuzumab alone. The Committee was unable to reconcile the differences in the outcomes reported in the MARIANNE and CLEOPATRA trials.*

The Committee, therefore, did not recommend the addition of pertuzumab to the complementary list of the Model List for the treatment of early-stage and metastatic HER2-positive breast cancer. *The Committee considered that the* ***available evidence did not demonstrate a clinically meaningful survival benefit in early-stage disease*** *and that there was important uncertainty surrounding the estimated magnitude of survival benefit in metastatic disease, with results seen in CLEOPATRA not replicated in other trials."*