Why the results of adjuvant pertuzumab in HER2-positive early breast cancer has been received as a mitigate success?

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Provenance: This is an invited Editorial commissioned by the Section Editor Hongcheng Zhu (Department of Radiation Oncology, The First Affiliated Hospital, Nanjing Medical University, Nanjing, China).

Comment on: von Minckwitz G, Procter M, de Azambuja E, *et al.* Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med 2017;377:122-31.

Submitted Sep 29, 2017. Accepted for publication Oct 10, 2017.
doi: 10.21037/cco.2017.10.07
View this article at: http://dx.doi.org/10.21037/cco.2017.10.07

All medical oncologists who attended the plenary session at ASCO 2005 remember the emotion provoked by the early release of the dramatic benefit resulting from the use of adjuvant trastuzumab (1,2). Since the incorporation of trastuzumab in the arsenal against metastatic disease, this therapeutic antibody has become the backbone of strategies in this setting (3-7). Despite this efficacy for advanced disease, few oncologists had foreseen such a dramatic magnitude of benefit with its use in the adjuvant setting for early breast cancer. In the editorial of the issue from the *New England Journal of Medicine* publishing adjuvants studies presented at ASCO, Hortobagyi emphasized that those results are "*not evolutionary but revolutionary*" (8). Since the advent of trastuzumab, the medical oncologist community has been impatient to experience such revolutions again.

Pertuzumab seemed to be a valuable candidate, able to push forward the results achieved by its predecessor, and partner, trastuzumab. The biological background supporting the association of trastuzumab and pertuzumab was fairly robust (9,10). In first line metastatic breast cancer, the CLEOPATRA study demonstrated a large survival benefit resulting from the addition of pertuzumab to the standard docetaxel-trastuzumab regimen (11). In the neoadjuvant setting, in addition to chemotherapy, dual inhibition by trastuzumab and pertuzumab nearly doubled the proportion of pathological complete response (pCR) (12). With longer follow-up, this study suggested a survival outcome benefit (13). Because a relationship between pCR and survival outcomes has been established, those results have allowed an accelerated regulatory approval in the US (in 2013) and Europe (in 2015) for the use of pertuzumab in the neoadjuvant setting (14). Importantly, the full approval in the US, was conditioned on the survival results of APHINITY trial (Adjuvant Pertuzumab and Herceptin in Initial Therapy in Breast Cancer; NCT01358877) (15).

All conditions seemed to favor the prediction of a dramatic benefit with the addition of pertuzumab in the early setting. In this large phase III study designed to prove this expectation, 4,805 patients were randomly assigned, after surgery, to receive six to eight cycles of chemotherapy plus 1 year of trastuzumab with either pertuzumab or placebo. Regarding the primary endpoint of invasive disease-free survival, the hazard ratio of 0.81 (95% CI, 0.66–1.00), significantly supported the benefit of pertuzumab (P=0.045). The incorporation of pertuzumab is not inconsequential with slightly more adverse events, including diarrhea [232 (9.8%) *vs.* 90 (3.7%)] but which rarely lead to treatment discontinuation. However, cardiac toxic effects, with long-term consequences might require attention even if the rates of heart failure were low in both treatment arms, 0.7% and 0.3% in the pertuzumab and placebo groups, respectively.

There are pros and cons regarding the perception of these results in the medical community. Addressing

the primary end point, invasive-disease–free survival, the findings were significant and APHINITY can claim to be a positive trial. The results support the capability of neo-adjuvant studies to predict the outcome of large adjuvant trials. APHINITY has validated the relationship between pCR benefit and the survival outcome observed in NeoSphere (12,13). Definitively, the addition of pertuzumab positively impacts the survival outcomes of patients with HER2-positive early breast cancer. The most effective duration of pertuzumab therapy need to be studied as well as the optimal duration of adjuvant trastuzumab has been assessed (16,17). Currently, it is difficult to decide whether patients who received a shorter duration of pertuzumab treatment in the neoadjuvant setting achieved the same benefit in terms of survival outcomes. Therefore, the standard of care might be to prolong the pertuzumab exposure up to 1 year based on APHINITY results.

Paradoxically, the positive results from APHINITY are disappointing, mainly because the expectations regarding the results reported by this study were so high. When compared with the dramatic benefit observed by adjuvant trastuzumab exposure and the results provided by the use of pertuzumab in metastatic disease and/or neoadjuvant treatment, the addition of pertuzumab in the adjuvant setting appears to be far less spectacular. The magnitude of the benefit regarding the absolute numbers in terms of disease recurrence events is not terrific with 171 out of 2,400 (7.1%) in the pertuzumab group compared with 210 out of 2,405 (8.7%) in the placebo group. Of course, the oncology community expected a larger treatment effect. These results were based on an analysis at 3 years of median follow-up and needs for longer follow-up are suggested. Continued follow-up of up to 10 years is planned and it will be important to assess overall survival, longer-term invasive disease free survival, and safety analysis. Nevertheless, taking into account that the benefit of adjuvant trastuzumab seems mainly a reduction in early recurrences, it seems unlikely that longer follow-up will drastically change the magnitude of the APHINITY results (6,16,18).

The authors of APHINITY highlight that the addition of pertuzumab is potentially practice-changing for those at the highest risk of relapse because, the overall results were driven by the subgroup of patients with node-positive breast cancer. In this subgroup, the results are more impressive with an HR 0.77 (95% CI, 0.62–0.96); P=0.02, leading to a 3-year invasive disease-free survival of 92.0% with pertuzumab compared to 90.2% in those receiving placebo. Whereas, in patients with node-negative breast cancer, the 3-year invasive disease-free survival rates were similar between the two arms with 32 and 29 events in the pertuzumab and placebo arms, respectively: 97.5% *vs.* 98.4% [HR 1.13 (0.68–1.86); P=0.64].

It is well established that subgroup analyses should be interpreted with caution, as they may induce overstated and misleading conclusions (19,20). Nevertheless, subgroup analyses are not always deleterious, or lead to invalid statistical conclusions. Some situations require adequate subgroup evaluation in order to adjust the validity of the overall conclusion, particularly when factors are known to influence outcome. When a positive interaction test is found, a variable treatment effect according to baseline characteristics may be observed. In this situation, it is highly debatable to defend a result in the overall population, rather than in a specifically defined subgroup (21). Without such heterogeneity and when properly planned a subgroup analysis can also provide valuable results. With rigorous subgroup analysis, the opportunity exists to present detailed data, better identifying the population, in which benefit exists, allowing identification of candidates for routine use. In APHINITY, no positive interaction test was reported, but since the beginning of the trial the selection of patients with node negative status and lower risk of recurrence was debatable. The credibility of this selection was based on the well-established efficacy of an adjuvant regimen containing trastuzumab as limiting the number of events counting for invasive disease free survival. After the accrual of around two-thirds of the study's population, an amendment was submitted to include only high risk cases with node-positive status in order to achieve the number of node-positive cases planned in the design. A pre-specified analysis of subgroups based on nodal involvement was scheduled. Obviously, the overall result was driven by the node-positive cases supporting the relevance of this pre-specified analysis. The results suggested evidence that the likelihood of benefit if any, benefit achieved by the addition of pertuzumab in node negative patients *vs.* trastuzumab containing regimen is limited. In contrast, in patients with node positive status, even more impressively when the nodal involvement was higher than 4, the addition of pertuzumab appeared to warrant the exposure. Ultimately, patients are best served when recommendations about clinical practice are guided by the strength of evidences, and in the present case, the analysis of the node-positive and node-negative subgroups allowed appropriate conclusions.

Unfortunately, the cost of trastuzumab may prohibit its use in some countries, leading to sub-optimal treatment, and

the routine addition of pertuzumab will be even less evenly distributed. The paradox is that it is these same low and middle-income countries with economic difficulties that most often have a higher incidence of cancers at a more advanced stage, requiring more active treatments. We must avoid for these countries the "double punishment", epidemiological and economic, explaining in large part a mortality excess.

The medical community should be concerned by the cost associated with a liberal prescription of pertuzumab even in the richest countries. Because the costs are high and the benefit concern a small proportion of patients, a selection of patients will be required. From the planned and valuable subgroup analysis, it is obvious that not every early breast cancer patient with HER2+ disease needs the combination biotherapy (22). Trastuzumab with chemotherapy remains the standard of care for a large group who achieved a definitive cure. The search for a possible reduction of aggressiveness in terms of trastuzumab duration and/or chemotherapy regimens has been undertaken and should be pursued in these favorable subgroups (17,23,24). On the other hand, to get the most value out of pertuzumab, we may propose its use in patients where there is the higher signal of benefit. Then, based on the subgroup findings in APHINITY, pertuzumab might be proposed in adjuvant therapy for patients with involved lymph nodes and who accept substantial toxic effects.

In the future, it will be not reasonable to add an unlimited number of therapies for all patients with HER2-positive disease selected on the basis of clinical characteristics. With this approach APHINITY might be one of the last huge trials including several thousands of patients without stringent biological criteria of selection. A better knowledge of HER2-positive breast cancer is needed even if the understanding of the heterogeneity HER2-positive disease still remains challenging. We know that despite being clinically defined by a specific gene amplification, HER2-positive tumours occur across the whole luminal-basal breast cancer spectrum rather than standing apart (25,26). Deciphering the tumoural genomic landscape, may allow the identification of biologic risk stratification, leading the identification of patients at truly high risk for which it is worth continuing to explore new therapies in clinical trials (27).

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Pivot X, Cox DG, Gligorov J. Why the results of adjuvant pertuzumab in HER2-positive early breast cancer has been received as a mitigate success? Chin Clin Oncol 2018;7(1):1. doi: 10.21037/cco.2017.10.07

