Editorial Commentary

Neoadjuvant dual anti-HER2 therapy for early breast cancer: where do we stand?

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Comment on: Shao Z, Pang D, Yang H, *et al.* Efficacy, safety, and tolerability of pertuzumab, trastuzumab, and docetaxel for patients with early or locally advanced ERBB2-positive breast cancer in Asia: the PEONY phase 3 randomized clinical trial. JAMA Oncol 2020;6:e193692.

Submitted Feb 22, 2020. Accepted for publication Mar 20, 2020.
doi: 10.21037/gs.2020.03.12
View this article at: http://dx.doi.org/10.21037/gs.2020.03.12

The recent published PEONY trial in the *JAMA Oncology* by Shao *et al.* reported a multicenter, double-blind, placebo-controlled randomized phase 3 trial studying the efficacy, safety and tolerability of pertuzumab along with trastuzumab and docetaxel in Asian patients with HER-2 positive non-metastatic breast cancer greater than 2 cm (1). Three hundred and twenty-nine patients were enrolled in the trial. Patients received 4 cycles of 3-weekly anti-HER2 therapy along with docetaxel in the neo-adjuvant setting followed by surgery followed by 3 cycles of FEC (fluorouracil, epirubicin and cyclophosphamide) and then 13 cycles of anti-HER2 therapy (similar to the one they received pre-surgery). The primary endpoint, pathologic complete response (pCR) rate demonstrated a statistically significant difference of 39.3% in the pertuzumab and trastuzumab group against a pCR of 21.8% in the placebo group (trastuzumab only). There was only a slightly higher incidence of serious adverse events in the pertuzumab group of 10.1% *vs.* 8.2% in the placebo group. The study design was clear and sound. pCR rate in a neo-adjuvant setting is a relevant prognostic endpoint with quick result and suggestion of a possible clinical gain.

Nevertheless, some important controversies must be assessed. pCR has been proposed as a surrogate endpoint for progression-free survival (PFS) and overall survival (OS), in trials, to expedite drug approval. It is clear from EBCTCG meta-analysis that responders (partial or complete) to systemic therapy do better than non-responders (2). The treatment in the neo-adjuvant setting helps to assess *in-vivo* chemosensitivity and the potential benefit of treatment. But pCR has never been validated as a trial-level surrogate for OS (3). So, the cardinal question remains if improved pCR translates into OS or PFS advantage for HER2 positive breast cancers. In the neoALTTO study, there was no difference in PFS or OS in the combination trastuzumab and lapatinib arm but patients achieving a pCR (irrespective of the treatment arm) had a better PFS and OS in comparison to those who didn't (4).

The PEONY study confirmed earlier results that the combination of chemotherapy (taxane based) with trastuzumab and pertuzumab gives more pCR in neo-adjuvant setting. In the NeoSphere study, Gianni reported an increase in pCR at 45% with trastuzumab and pertuzumab *vs.* 29% trastuzumab only in 2012 (5) but the follow-up NeoSphere study published in 2016 showed only a marginal benefit in the PFS after 5 years of the combination therapy over trastuzumab alone (86% *vs.* 81%). In addition, the confidence intervals were wide and overlapping to achieve significance (6). Other trials such as Tryphaena cardiac safety study have addressed the superiority of dual anti-HER2 therapy in achieving a significantly higher pCR with addition of pertuzumab (7). In this study, patients who achieved pCR also had improved disease-free survival (DFS). Although the combination with pertuzumab has never been shown to increase OS, NICE recommended dual therapy in the UK for high-risk breast cancer patients with involved lymph nodes (NICE guidance TA569).

Independent of better OS, increasing pCR could have potential advantages.

First, de-escalation of chemotherapy could be possible, avoiding anthracycline toxicity after obtaining a pCR with a taxane combination and a dual-blocker as in the PEONY trial.

Second, pertuzumab could be perhaps omitted after surgery once the pathologist has confirmed pCR. This is particularly relevant in Asian countries with limited resources and insurance coverage (8).

Third, de-escalation of surgery with a higher rate of breast conservation or even omitting surgery could become possible. A high pCR and greater than 50% correlation between complete radiological response and pCR has been seen in the retrospective review of 91 clinical cases audited in Oxford, suggesting a significant potential for change in surgical plan after neoadjuvant chemotherapy (9).

Another important issue is the cost-effectiveness of the addition of pertuzumab, especially in an Asian context. The addition of pertuzumab has only small clinical benefit and no proven significant survival advantage. Most big trials (NeoSphere) were not powered to provide long-term benefit (6) and others (Tryphaena and Berenice) concentrated on safety and cardiotoxicity and lacked the control arm (7,10). The adjuvant Aphinity trial, reported at San Antonio Breast Cancer Symposium in 2019, that only lymph node positive patients attain a better 6-year invasive DFS with 87.9% in the pertuzumab group compared with 83.4% in the placebo group. A slightly higher incidence of toxicity, merely by a higher degree of diarrhea 38.5% *vs.* 16.4% was reported in the pertuzumab group (11,12). The cost of adding pertuzumab to node negative HER2-positive patients with early breast cancer could be difficult to justify in the absence of evidence of significant long-term benefit.

Last but not least issue, is criticism on methodology, as PEONY study is industry sponsored with a major role played by the company in study design, data interpretation and writing assistance. An academic study would be more appropriate. It is also unclear if Chinese patients represent the Asian population adequately, with no patients of Indian origin included in the study.

To conclude, strategies of combining and optimizing HER2-targeted therapies could potentially improve outcomes for high-risk HER2-positive breast cancer patients but may in essence allow de-escalation of treatment in many patients, potentially sparing a lot of patients from unnecessary treatments and their related toxicities. The need for anthracyclines, number of cycles of taxane and the number of cycles of trastuzumab and pertuzumab must be assessed.

The future of HER2 patients seems anyways bright. The recent findings of additional benefit of trastuzumab emtansine (T-DM1) in the event of not obtaining a pCR in the neo-adjuvant setting (13), the introduction of trastuzumab deruxtecan (14) and in addition, promising benefit of oral HER2-selective small molecules as tucatininb (15) and neratinib would lead to further improvements in all settings but it is obligatory to critically evaluate the real benefits, certainly in the adjuvant setting.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Editorial Office, *Gland Surgery*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs.2020.03.12). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Roy PG, Verhoeven D. Neoadjuvant dual anti-HER2 therapy for early breast cancer: where do we stand? Gland Surg 2020;9(5):1167-1169. doi: 10.21037/gs.2020.03.12

