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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

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IMPORTANCE Prospective assessment of treatments known to benefit patients in global clinical trials in specific racial groups is essential.

OBJECTIVE To compare the efficacy, safety, and tolerability of adding pertuzumab to trastuzumab and docetaxel vs placebo, trastuzumab, and docetaxel in Asian patients with ERBB2-positive early or locally advanced breast cancer.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, double-blind, placebo-controlled phase 3 trial enrolled 329 women with ERBB2-positive early (T2-3, N0-1, M0) or locally advanced breast cancer (T2-3, N2 or N3, M0; T4, any N, M0) and primary tumor larger than 2 cm from March 14, 2016, to March 13, 2017. Analysis of the primary end point was performed on an intention-to-treat basis.

INTERVENTIONS Before surgery, patients received 4 cycles of intravenous pertuzumab (840-mg loading dose and 420-mg maintenance doses), trastuzumab (8-mg/kg loading dose and 6-mg/kg maintenance doses), and docetaxel (75 mg/m^2) or intravenous placebo, trastuzumab, and docetaxel every 3 weeks. After surgery, patients received 3 cycles of intravenous fluorouracil, epirubicin, and cyclophosphamide followed by 13 cycles of the same intravenous anti-ERBB2 therapy (pertuzumab and trastuzumab or placebo and trastuzumab) for up to 1 year.

MAIN OUTCOMES AND MEASURES The primary end point was independent review committee–assessed total pathologic complete response rate. The 2-sided Cochran-Mantel-Haenszel test, stratified by disease category and hormone receptor status, was used to compare rates between treatment groups.

RESULTS In total, 329 female patients were randomized (pertuzumab, 219; and placebo, 110; mean [SD] age, 48.8 [9.5] years). In the intention-to-treat population, total pathologic complete response rates were 39.3% (86 of 219) in the pertuzumab group and 21.8% (24 of 110) in the placebo group (difference, 17.5% [95% CI, 6.9%-28.0%]; P = .001). Of the most common grade 3 or higher adverse events, there was a higher incidence of neutropenia in the pertuzumab group (83 of 218 [38.1%] vs 36 of 110 [32.7%]). Serious adverse events were reported in 10.1% of patients (22 of 218) in the pertuzumab group and 8.2% of patients (9 of 110) in the placebo group.

CONCLUSIONS AND RELEVANCE Treatment with pertuzumab, trastuzumab, and docetaxel resulted in a statistically significant improvement in the total pathologic complete response rate vs placebo, trastuzumab, and docetaxel for the neoadjuvant treatment of ERBB2-positive early or locally advanced breast cancer in Asian patients. Safety data were in line with the known pertuzumab safety profile and generally comparable between treatment groups. The PEONY trial adds to the totality of data showing the benefit of the pertuzumab regimen.

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Supplemental content

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Efficacy of dual ERBB2 blockade with pertuzumab and trastuzumab plus chemotherapy in the neoadjuvant setting for early, locally advanced, or inflammatory ERBB2-positive breast cancer was demonstrated in the phase 2 NeoSphere study (ClinicalTrials.gov identifier: NCT00545688), which found significantly increased breast pathologic complete response (ypT0/is) vs trastuzumab and chemotherapy.[1] Total pathologic complete response (tpCR; absence of residual invasive cancer in the breast and lymph nodes [ypT0/is, ypN0]) was also increased.[1] Dual ERBB2 blockade and chemotherapy was well tolerated,[1] and similar cardiac safety has been observed in the neoadjuvant setting.[2,3]

Despite extensive data, trastuzumab use for breast cancer in China remains low,[4] and the proportion of Asian patients in previous pertuzumab studies was less than 25%. The benefit of dual ERBB2-targeted neoadjuvant therapy in these patients has not yet been fully characterized.

Therefore, pertuzumab, trastuzumab, and chemotherapy in Asian patients with early breast cancer (EBC) or locally advanced breast cancer (LABC) in the neoadjuvant setting required further evaluation in a phase 3 study. We present primary efficacy and safety results from the neoadjuvant treatment period of the PEONY trial.

Key Points

Question Do Asian patients with ERBB2-positive early or locally advanced breast cancer benefit from the addition of pertuzumab to trastuzumab and docetaxel in the neoadjuvant setting, compared with placebo, trastuzumab, and docetaxel?

Findings In this randomized clinical trial of 329 women with early or locally advanced breast cancer, total pathologic complete response rates were 39.3% with pertuzumab and 21.8% with placebo, a significant difference. Safety data were generally comparable between groups.

Meaning Pertuzumab, trastuzumab, and docetaxel significantly improved total pathologic complete response rate vs placebo, trastuzumab, and docetaxel in the neoadjuvant setting; this study adds to the totality of the data showing the benefit of the pertuzumab regimen.

Methods

Study Design

The PEONY trial (NCT02586025) is a randomized, multicenter, double-blind, placebo-controlled, phase 3 trial in an Asian population at 23 cancer centers. Full details of the study design, eligibility criteria, treatment, and outcomes are provided in the trial protocol in Supplement 1 and the eFigure in Supplement 2; a full list of investigators is in eAppendix 1 in Supplement 2 and measurement of clinical response is in eAppendix 2 in Supplement 2. The PEONY trial is being conducted in full conformance with the International Conference on Harmonisation E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki,[5] or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study complies with the requirements of the International Conference on Harmonisation E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). The protocol, written informed consent forms, any information to be given to the patient, and relevant supporting information from each participating institution were submitted to the institutional review board and/or ethics committee (Supplement 1) by the principal investigator (Z.S.), and reviewed and approved by the institutional review board and/or ethics committee before the study was initiated.

Patients with ERBB2-positive EBC (T2-3, N0-1, M0) or LABC (T2-3, N2-N3, M0; T4, any N, M0) and primary tumors larger than 2 cm were randomized 2:1 to receive 4 cycles of intravenous pertuzumab (840-mg loading dose and 420-mg maintenance doses), trastuzumab (8-mg/kg loading dose and 6-mg/kg maintenance doses), and docetaxel (75 mg/m^2) or intravenous placebo, trastuzumab, and docetaxel every 3 weeks before surgery. After surgery, patients received 3 cycles of intravenous fluorouracil, epirubicin, and cyclophosphamide (a standard regimen in the adjuvant setting) followed by 13 cycles of the same intravenous anti-ERBB2 therapy (pertuzumab and trastuzumab or placebo and trastuzumab; separated from fluorouracil, epirubicin, and cyclophosphamide in the interests of safety) for up to 1 year. The primary end point was independent review committee–assessed tpCR rate when patients completed surgery.

Statistical Analysis

A total of 328 patients were planned, to provide 85% power at a 2-sided significance level of .05 to detect an absolute difference in tpCR rates of 15% between groups in the intention-to-treat population. The assumed tpCR rates were 35% in the pertuzumab group and 20% in the placebo group; the minimum detectable difference, 9.8%. $P < .05$ was considered significant.

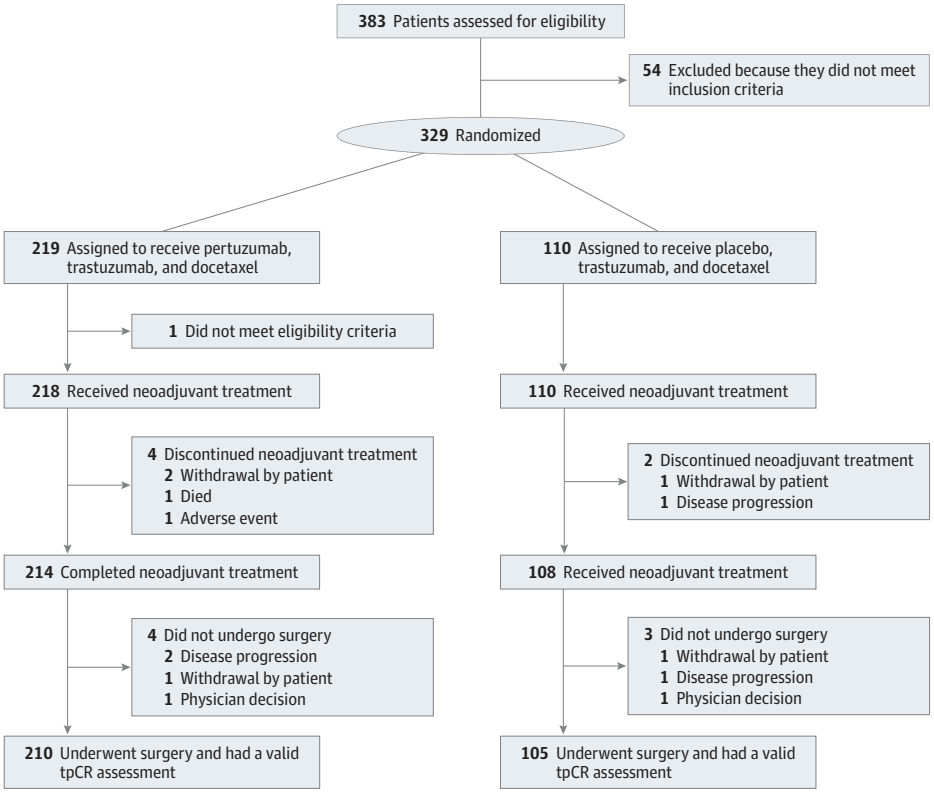
The 95% CIs for 1 sample binomial were calculated using the Clopper-Pearson method; approximate 95% CIs for differences between rates, using the Hauck-Anderson method. The 2-sided Cochran-Mantel-Haenszel test, stratified by disease category (EBC or LABC) and hormone receptor status (estrogen receptor positive and/or progesterone receptor positive, or negative for both), was used to compare tpCR rates between groups. Patients with missing assessments were considered nonresponders. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

Patients

A total of 329 patients were enrolled from March 14, 2016, to March 13, 2017 (pertuzumab group, 219; and placebo group, 110). The data cutoff date was October 23, 2017. **Figure 1** shows patient dispositions. Baseline demographics and disease characteristics were generally well balanced (eTable 1 in Supplement 2). Most patients received 4 treatment cycles (eTable 2 in Supplement 2).

Figure 1. CONSORT Diagram



tpCR indicates total pathologic complete response.

Efficacy

Independent review committee–assessed tpCR rates were 39.3% (86 of 219) in the pertuzumab group and 21.8% (24 of 110) in the placebo group (intention-to-treat populations), for a difference of 17.5% (95% CI, 6.9%-28.0%; P = .001) (**Figure 2**A; subgroup rates are shown in Figure 2B). The rate ratio (pertuzumab group vs placebo group) was 1.80 (95% CI, 1.22-2.66).

Objective responses were achieved by 194 of 219 patients in the pertuzumab group (88.6%; 95% CI, 83.6%-92.5%) and 86 of 110 patients in the placebo group (78.2%; 95% CI, 69.3%-85.5%), for a difference of 10.4% (95% CI, 1.1%-19.7%). Clinical complete response rates were achieved by 24 of 219 patients in the pertuzumab group (11.0%; 95% CI, 7.2%-15.9%) vs 11 of 110 patients in the placebo group (10.0%; 95% CI, 5.1%-17.2%), and clinical partial response rates were achieved by 170 of 219 patients in the pertuzumab group (77.6%; 95% CI, 71.5%-83.0%) vs 75 of 110 patients in the placebo group (68.2%; 95% CI, 58.6%-76.7%).

Safety

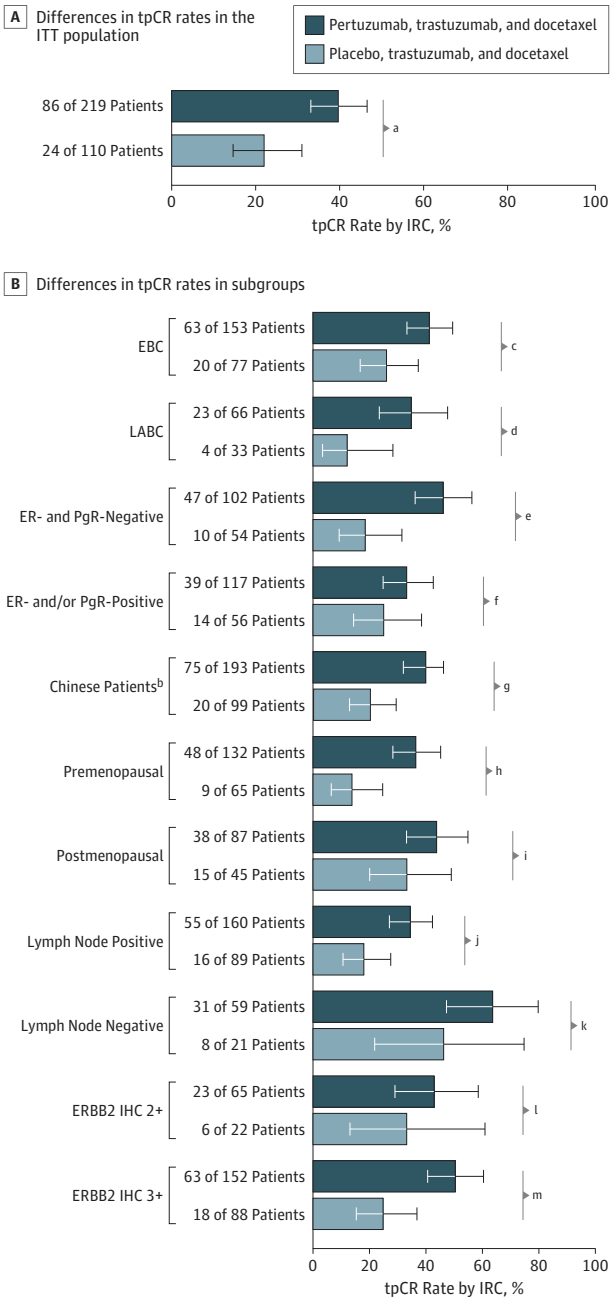
Safety data are summarized in the **Table**. Incidences of most of the common adverse events were similar between groups. There was a higher incidence of diarrhea in the pertuzumab group than in the placebo group (84 of 218 [38.5%] vs 18 of 110 [16.4%]); most was grade 1 (58 of 218 [26.6%] vs 13 of 110 [11.8%] in the placebo group) or grade 2 (24 of 218 [11.0%] vs 5 of 110 [4.5%]), while 2 of 218 patients in the pertuzumab group (0.9%) had grade 3 events. Of the most common grade 3 or higher adverse events, there was a higher incidence of neutropenia in the pertuzumab group (83 of 218 [38.1%] vs 36 of 110 [32.7%]). Serious adverse events were reported in 10.1% of patients (22 of 218) in the pertuzumab group and 8.2% of patients (9 of 110) in the placebo group.

Discussion

The PEONY trial met its primary end point, providing, to our knowledge, the first efficacy data from a randomized, placebo-controlled, phase 3 study of the addition of pertuzumab vs placebo to trastuzumab and docetaxel in the neoadjuvant setting in an Asian population with ERBB2-positive EBC or LABC; adding pertuzumab resulted in a statistically significant improvement in the tpCR rate. Subgroup analyses showed a consistent trend of treatment benefit in the pertuzumab group. These data are consistent with previous pertuzumab studies and support the conclusion that pertuzumab is efficacious in ERBB2-positive EBC across races.

In the neoadjuvant setting, studies of pertuzumab, trastuzumab, and chemotherapy have reported tpCR or breast pathologic complete response rates of 40.9% to 63.6% (although in some studies, patients received ≥4 cycles of chemotherapy before surgery).[2,3,6-8] In the PEONY trial, tpCR rates as determined by independent review committee were 39.3% with 4 cycles of pertuzumab, trastuzumab, and docetaxel

Figure 2. Efficacy Data



A, Total pathologic complete response (tpCR) rates as determined by independent review committee (IRC) in the intention-to-treat (ITT) population (stratified analysis). B, tpCR rates as determined by independent review committee in subgroups (unstratified). IHC 2+ and IHC 3+ are levels of immunohistochemistry (IHC) staining. Error bars represent 95% CIs. EBC indicates early breast cancer; ER, estrogen receptor; LABC, locally advanced breast cancer; and PgR, progesterone receptor.

[a] Difference, 17.5% (95% CI, 6.9%-28.0%). [b]Defined as those from mainland China or Taiwan. [c]Difference, 15.2% (95% CI, 2.0%-28.4%). [d]Difference, 22.7% (95% CI, 5.0%-40.4%). [e]Difference, 27.6% (95% CI, 12.4%-42.8%). [f]Difference, 8.3% (95% CI, −6.9% to 23.5%). [g]Difference, 18.7% (95% CI, 7.6%-29.7%). [h]Difference, 22.5% (95% CI, 9.9%-35.1%). [i]Difference, 10.3% (95% CI, −8.2% to 28.9%). [j]Difference, 16.4% (95% CI, 4.9%-27.9%). [k]Difference, 14.5% (95% CI, −12.8% to 41.7%). [l]Difference, 8.1% (95% CI, −16.5% to 32.8%). [m]Difference, 21.0% (95% CI, 8.9%-33.1%).

Table. Safety Summary (Safety Population)

Safety Data	Patients, No. (%)	
	Pertuzumab, Trastuzumab, and Docetaxel (n = 218)	Placebo, Trastuzumab, and Docetaxel (n = 110)
10 Most common AEs		
Alopecia	107 (49.1)	54 (49.1)
Neutropenia	105 (48.2)	49 (44.5)
Leukopenia	92 (42.2)	43 (39.1)
Diarrhea	84 (38.5)	18 (16.4)
Anemia	53 (24.3)	30 (27.3)
Alanine aminotransferase increased	49 (22.5)	26 (23.6)
Nausea	45 (20.6)	21 (19.1)
Aspartate aminotransferase increased	37 (17.0)	22 (20.0)
Pyrexia	31 (14.2)	11 (10.0)
Upper respiratory tract infection	33 (15.1)	7 (6.4)
Infusion-related reactions[a]	48 (22.0)	10 (9.1)
Grade ≥3 AEs	106 (48.6)	46 (41.8)
Most common grade ≥3 AEs (≥3% of patients)		
Neutropenia	83 (38.1)	36 (32.7)
Leukopenia	45 (20.6)	21 (19.1)
Serious AEs	22 (10.1)	9 (8.2)
Most common serious AE: febrile neutropenia	4 (1.8)	1 (0.9)
Deaths	1 (0.5)[b]	0
Heart failure (NYHA functional classification III or IV)	0	0
Significant LVEF decline events (≥10 percentage points from baseline and to <50%)	0	0

Abbreviations: AE, adverse event; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

[a] Pooled term of anaphylaxis-related and hypersensitivity-related AEs occurring on the same day as pertuzumab infusion.

[b] Due to suicide on day 15, which was not related to pertuzumab, trastuzumab, or docetaxel.

before surgery. This finding may explain the relatively lower tpCR rates seen in the PEONY trial and NeoSphere trial vs other studies. However, the timing of chemotherapy in relation to surgery is not expected to affect long-term outcomes.[9] The PEONY trial and NeoSphere trial differ in that patients randomized to pertuzumab-containing study groups in the NeoSphere trial did not receive pertuzumab after surgery, only trastuzumab and chemotherapy, to complete 1 year of treatment, whereas patients in the PEONY trial received trastuzumab or pertuzumab and trastuzumab per randomization to complete 1 year of treatment. Although progression-free survival and disease-free survival at 5-year follow-up in the NeoSphere trial showed large, overlapping CIs, they supported the primary end point,[10] suggesting that adding pertuzumab to trastuzumab and docetaxel in the neoadjuvant setting is potentially beneficial with respect to long-term outcomes. The PEONY trial's long-term efficacy outcomes will provide information regarding the significance of pathologic complete response in the context of a complete anti-ERBB2 regimen (approximately 1 year of therapy) of pertuzumab and

trastuzumab or trastuzumab, although it is not powered for survival end points. Achieving pathologic complete response after neoadjuvant therapy is likely to be prognostic for long-term clinical benefit.[11]

Safety data were in line with the known pertuzumab safety profile and generally comparable between groups. Diarrhea and infusion-related reactions were more common with pertuzumab. Diarrhea is common with pertuzumab, and was less frequent in the PEONY trial than in the NeoSphere trial.[1] Cardiac safety is an important consideration when treating patients with ERBB2-targeted therapy. In the PEONY trial, no primary or secondary cardiac events were observed during the neoadjuvant treatment period, consistent with the low rates reported in the NeoSphere trial.[1]

Strengths and Limitations

The strengths of the PEONY trial include the placebo-controlled design and assessment of tpCR rates as determined by independent review committee (not used in the NeoSphere trial). Owing to the short follow-up period at the clinical cutoff date, the total numbers of events for the secondary end points, such as event-free survival and overall survival, were too limited to be shown at this analysis.

Conclusions

Adding pertuzumab to trastuzumab and docetaxel resulted in a statistically significant improvement in tpCR vs placebo, trastuzumab, and docetaxel for the neoadjuvant treatment of ERBB2-positive EBC or LABC in Asian patients, with safety data in line with the known pertuzumab safety profile. The PEONY trial adds to the totality of the data showing the benefit of pertuzumab and trastuzumab with chemotherapy in ERBB2-positive EBC.

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Author Contributions: Drs Zhou and Eng-Wong had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Shao, J. Li, Zhou, Althaus, Eng-Wong.
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