Final overall survival (OS) analysis of PHEREXA: A randomized phase III trial of trastuzumab (H) + capecitabine (X) ± pertuzumab (P) in patients with HER2-positive metastatic breast cancer (MBC) who experienced disease progression during or after H-based therapy

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Background

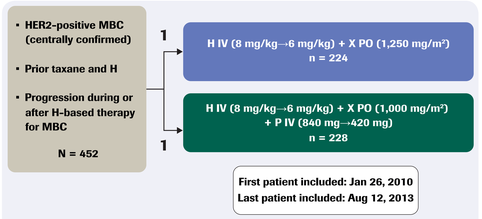
- H + chemotherapy + P is highly effective for the first-line treatment of HER2-positive MBC[1,2] and for high-risk HER2-positive early BC.[3]
- The PHEREXA study (NCT01026142) evaluated H + X ± P in patients with HER2-positive MBC who received a prior taxane and progressed during or after H-based therapy.[4]
  - The study rationale was based on the German Breast Group 26 trial, which showed that continuing H with X after progressing on an H-containing regimen increased response and time to progression compared with X alone, without an increase in toxicity.[5]
  - In addition, comprehensive HER2 signaling blockade with H + P has been shown to be active in patients who received prior H therapy.[6]
- In the primary analysis of PHEREXA (clinical cutoff: May 29, 2015), adding P to H + X did not significantly improve independent review facility-assessed progression-free survival (IRF-PFS; the primary endpoint).[4]
  - IRF-PFS hazard ratio (HR) 0.82; 95% confidence interval (CI) 0.65–1.02; p = .0731.
  - An 8-month increase in median OS (secondary endpoint) from 28.1 to 36.1 months was observed with P at an interim OS analysis at the time of the primary IRF-PFS analysis, but due to hierarchical testing of IRF-PFS, and subsequently of OS (to control type I error), statistical significance could not be claimed.
  - No new safety signals were identified.
- We now report the final prespecified analysis of the secondary endpoints of OS, investigator-assessed PFS (INV-PFS), and safety.

Methods

Study design

- PHEREXA is a multicenter, open-label, randomized phase III study,[4] the design of which is shown in Figure 1.
  - H and P were given intravenously every 3 weeks. X was given orally twice daily (2 weeks on, 1 week off, every 3 weeks).[4]

Figure 1. Study design.[7]



Treatment was given until disease progression, unmanageable toxicity, or patient request for discontinuation. Stratification was by prior central nervous system disease, measurable vs. nonmeasurable disease, and response to first-line H. The study was conducted in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Each participant provided written informed consent. An independent ethics committee for each participating site approved the protocol and any amendments. Safety was monitored by an independent data monitoring committee, which also made recommendations regarding study continuation.
H, trastuzumab; IV, intravenous; MBC, metastatic breast cancer; P, pertuzumab; PO, oral; X, capecitabine.
Adapted with permission from Urruticoechea A, *et al.* ASCO 2016; Abstract 504 and associated oral presentation.[7]

- The end of study was defined as whichever of the following occurred first: results from the interim analysis of OS met the predefined criteria for statistical significance and demonstrated a difference between treatment groups that was considered clinically meaningful, or approximately 300 deaths (67% of enrolled patients) were reported, or the trial was terminated by the sponsor. The sponsor decided to end the study early, close to the time of the planned final OS analysis, given the primary endpoint was not met.
- OS and INV-PFS were assessed in the intention-to-treat population (all randomly assigned patients).
  - Median INV-PFS for each arm was estimated using the Kaplan-Meier approach; the hazard ratios between the two arms and the 95% confidence intervals, using the stratified Cox proportional hazards regression model (stratified by random assignment stratification factors).
- Adverse events (AEs) were assessed in the safety population (patients who received ≥ 1 dose of study drug).
- All results are descriptive.

Results

Patients

- Clinical cutoff was Sep 20, 2017.
- Median time on study, including post-treatment follow-up, was 23.2 months in the H + X arm and 33.0 months in the H + X + P arm.
- Demographics and baseline characteristics were generally similar between arms.[4]
  - Slightly over half of patients (55%) had hormone receptor-positive disease.
  - Sixty-five percent had visceral disease.
  - Prior H exposure was generally comparable between arms.
  - All patients received first-line H for MBC; 25% of these also received H in the early setting.
  - Approximately 40% of patients had > 12 months' response duration in the first line (these patients were classed as good responders to H).
  - Time from last H dose initiation of treatment in PHEREXA was the same in each arm.
- Patient withdrawals from study treatment are shown in Table 1.
  - At clinical cutoff, all patients had discontinued study treatment, primarily due to disease progression.
  - During the post-treatment follow-up period, five patients in the H + X arm went on to receive standard of care, and 11 patients in the H + X + P arm crossed over to the PEREX study (NCT02320435) to continue P treatment per the PHEREXA protocol after the study closed.

Table 1. Patient withdrawals from study treatment (safety population).

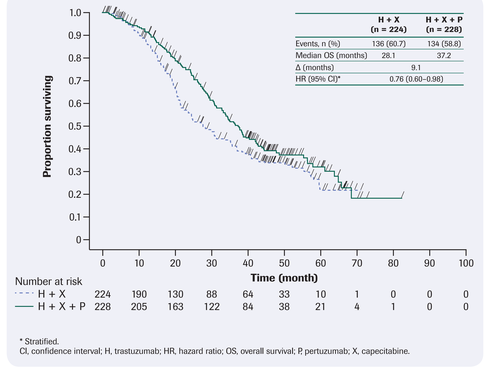
Patients, n (%)	H + X (n = 218)	H + X + P (n = 228)
Reason for withdrawal		
Safety	**22 (10.1)**	**18 (7.9)**
Adverse event	22 (10.1)	17 (7.5)
Death	**0**	**1 (0.4)**
Non-safety	**196 (89.9)**	**210 (92.1)**
Disease progression	**174 (79.8)**	**190 (83.3)**
Violation of selection criteria at entry	0	4 (1.8)
Refused treatment	16 (7.3)	8 (3.5)
Administrative/other	6 (2.8)	8 (3.5)
Total	**218 (100)**	**228 (100)**

H, trastuzumab; P, pertuzumab; X, capecitabine.

Efficacy

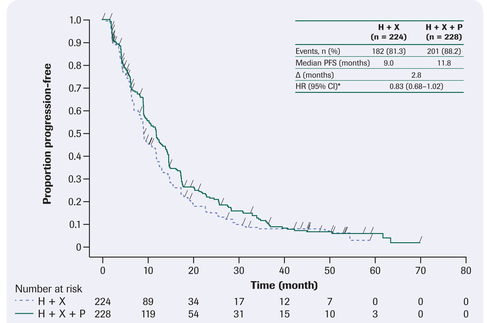
- The final analysis of OS (HR 0.76; 95% CI 0.60–0.98) indicated an increase in median OS of 9.1 months (28.1 months in the H + X arm vs. 37.2 months in the H + X + P arm) (Figure 2).
  - This was not statistically significant due to hierarchical testing.
- INV-PFS (HR 0.83; 95% CI 0.68–1.02) showed an increase in median PFS of 2.8 months (9.0 months in the H + X arm vs. 11.8 months in the H + X + P arm) (Figure 3).

Figure 2. Final OS (intention-to-treat population).



* Stratified.
CI, confidence interval; H, trastuzumab; HR, hazard ratio; OS, overall survival; P, pertuzumab; X, capecitabine.

Figure 3. INV-PFS (intention-to-treat population).



* Stratified.
CI, confidence interval; H, trastuzumab; HR, hazard ratio; P, pertuzumab; PFS, progression-free survival; X, capecitabine.

Safety

- The safety and tolerability of H + X + P was comparable to that of H + X in terms of the incidence and severity of any-grade AEs (the majority were grade 1–2 in severity), serious AEs, discontinuations due to AEs, and AEs leading to death (Table 2).
- There were 129 deaths in the H + X arm and 127 deaths in the H + X + P arm during the post-treatment period; most were due to disease progression (Table 3).

Table 2. Safety overview (safety population).

Patients (%)	H + X (n = 218)	H + X + P (n = 228)
Any AE	**214 (98.2)**	**222 (97.4)**
Most common AEs (incidence ≥ 10% in either arm, with ~5% difference between arms)		
Diarrhea	130 (59.6)	159 (69.7)
Nausea	98 (45.0)	88 (38.6)
Hand–foot syndrome	160 (73.4)	129 (56.6)
Rash	11 (5.0)	36 (15.8)
Neutropenia	39 (17.9)	30 (13.2)
Insomnia	12 (5.5)	23 (10.1)
NCI-CTCAE grade ≥ 3 AE	**131 (60.1)**	**122 (53.5)**
Most common NCI-CTCAE grade ≥ 3 AE (incidence ≥ 5% in either arm)		
Diarrhea	22 (10.1)	37 (16.2)
Hand–foot syndrome	48 (22.0)	23 (10.1)
Neutropenia	13 (6.0)	9 (3.9)
Serious AE	**53 (24.3)**	**58 (25.4)**
AE leading to discontinuation of any study treatment	**42 (19.3)**	**50 (21.9)**
AE resulting in death	**2 (0.9)***	**1 (0.4)†**

* Cardiac arrest and subarachnoid hemorrhage; † General physical health deterioration.
AE, adverse event; H, trastuzumab; NCI-CTCAE, National Cancer Institute – Common Terminology Criteria for Adverse Events; P, pertuzumab; X, capecitabine.

Table 3. Deaths during the post-treatment period (safety population).

	H + X (n = 218)	H + X + P (n = 228)
Total number of deaths, patients (%)	**129 (59.2)**	**127 (55.7)**
Disease progression	121 (55.5)	119 (52.2)
"Death"	4 (1.8)	3 (1.3)
Other	4 (1.8)	5 (2.2)

There were four causes recorded as "other" since the primary analysis: "sepsis," "interstitial lung disease," "lung neoplasm malignant," and "lymphangiosis carcinomatosa."
H, trastuzumab; P, pertuzumab; X, capecitabine.

- The incidence of symptomatic left ventricular systolic dysfunction (LVSD) and asymptomatic LVSD events was higher in the H + X + P arm than in the H + X arm (Table 4).
- There were no new symptomatic LVSD events with 27 months' extra follow-up since the primary analysis (0 patients in the H + X arm and 5 [2.2%] in the H + X + P arm[4]) (Table 4).
  - At clinical cutoff, four of the five symptomatic LVSD events had resolved.
  - In one patient, the left ventricular ejection fraction (LVEF) value at the second follow-up visit was 42% (local reading); however, the patient was then lost to follow-up before the end of the study and no additional LVEF assessments are available.

Table 4. Cardiac safety (safety population).

	H + X (n = 218)	H + X + P (n = 228)
Symptomatic LVSD recorded as an AE, patients (%)*	**0**	**5 (2.2%)**
NYHA Class II	0	3 (1.3)
NYHA Class III	0	1 (0.4)
NYHA Class IV	0	1 (0.4)
Asymptomatic LVEF drops to ≥ 10% points below baseline and value < 50%, patients (%)	**6 (2.8)**	**13 (5.7)**
Events, n	7	16
Asymptomatic LVEF drop requiring treatment or leading to discontinuation, patients (%)	**1 (0.5)**	**1 (0.4)**
Events, n	1	1

* All NCI-CTCAE grade 3.
AE, adverse event; H, trastuzumab; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; NCI-CTCAE, National Cancer Institute – Common Terminology Criteria for Adverse Events; NYHA, New York Heart Association; P, pertuzumab; X, capecitabine.

Conclusions

- Although the primary endpoint was not met,[4] with a median OS of 37.2 months in the H + X + P arm vs. 28.1 months in the H + X arm (a 9.1-month increase), the final analysis of OS in PHEREXA was consistent with the interim OS analysis[4] and supports clinical activity of H + P being maintained with longer follow-up.
- INV-PFS was consistent with the primary analysis,[4] with median of 9.0 months in the H + X arm and 11.8 months in the H + X + P arm.
- Overall, the safety profile of the H + X + P regimen was consistent with previous studies of P.
  - No new safety signals were observed.
- The incidence of symptomatic LVSD did not change from the primary analysis,[4] which confirms the existing cardiac safety profile of H + P.
- There was no evidence of late cardiac toxicity.

Acknowledgments

We would like to thank all the patients who participated in the trial, and their families, the investigators, clinicians, and research staff at the 171 sites in 22 countries.

Funding for this analysis was provided by F. Hoffmann-La Roche Ltd.

Support for third-party writing assistance for this poster, furnished by Daniel Clyde, PhD of Health Interactions, was provided by F. Hoffmann-La Roche Ltd.

Disclosures

AU: Consulting or advisory role (F. Hoffmann-La Roche Ltd, Eisai; self); travel/accommodation/expenses (F. Hoffmann-La Roche Ltd, Amgen; self). S-AI: Research funding (AstraZeneca; self); consulting or advisory role (Novartis, F. Hoffmann-La Roche Ltd, Pfizer, and Hannic; self). HD: Employment (Roche Products Limited; self). TBC: Employment (F. Hoffmann-La Roche Ltd; self); stock or other ownership (F. Hoffmann-La Roche Ltd; self); patents, royalties, or other IP (F. Hoffmann-La Roche Ltd; self). SH: Employment (Roche Products Limited; self); stock or other ownership (F. Hoffmann-La Roche Ltd; self); patents, royalties or other IP (Roche Products Limited; self). JE-W: Employment (Genentech, Inc./F. Hoffmann-La Roche Ltd; self); stock or other ownership (Genentech, Inc./F. Hoffmann-La Roche Ltd; self); patents, royalties or other IP (Genentech, Inc./F. Hoffmann-La Roche Ltd; self). MM: Consulting or advisory role (F. Hoffmann-La Roche Ltd; self); speakers' bureau (Novartis; self); expert testimony (Novartis; self); travel/accommodation/expenses (F. Hoffmann-La Roche Ltd; self). No other authors have any conflicts of interest to declare.

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