

6. Gathinji M, McGirt MJ, Attenello FJ et al Association of preoperative depression and survival after resection of malignant brain astrocytoma. *Surg Neurol* 2009; 71(3): 299–303.
7. Hjerl K, Andersen EW, Keiding N et al Depression as a prognostic factor for breast cancer mortality. *Psychosomatics* 2003; 44(1): 24–30.
8. Hill J, Holcombe C, Clark L et al Predictors of onset of depression and anxiety in the year after diagnosis of breast cancer. *Psychol Med* 2011; 41(7): 1429–1436.
9. Llorente MD, Burke M, Gregory GR et al Prostate cancer: a significant risk factor for late-life suicide. *Am J Geriatr Psychiatry* 2005; 13(3): 195–201.
10. Misono S, Weiss NS, Fann JR et al Incidence of suicide in persons with cancer. *J Clin Oncol* 2008; 26(29): 4731–4738.
11. O'Rourke RW, Diggs BS, Spight DH et al Psychiatric illness delays diagnosis of esophageal cancer. *Dis Esophagus* 2008; 21(5): 416–421.
12. Hashimoto N, Isaka N, Ishizawa Y et al Surgical management of colorectal cancer in patients with psychiatric disorders. *Surg* 2009; 39(5): 393–398.
13. Edwards B, Clarke V. The psychological impact of a cancer diagnosis on families: the influence of family functioning and patients' illness characteristics on depression and anxiety. *Psychooncology* 2004; 13(8): 562–576.
14. Bruce M. A systematic and conceptual review of posttraumatic stress in childhood cancer survivors and their parents. *Clin Psychol Rev* 2006; 26(3): 233–256.
15. Ozono S, Saeki T, Mantani T et al Factors related to posttraumatic stress in adolescent survivors of childhood cancer and their parents. *Support Care Cancer* 2007; 15(3): 309–317.
16. Vanderwerker LC, Laff RE, Kadan-Lottick NS et al Psychiatric disorders and mental health service use among caregivers of advanced cancer patients. *J Clin Oncol* 2005; 23(28): 6899–6907.
17. Chou FH-C, Tsai K-Y, Su C-Y et al The incidence and relative risk factors for developing cancer among patients with schizophrenia: a nine-year follow-up study. *Schizophr Res* 2011; 129(2–3): 97–103.
18. Roe CM, Behrens MI, Xiong C et al Alzheimer disease and cancer. *Neurology* 2005; 64(5): 895–898.
19. Tran E, Rouillon F, Loze J-Y et al Cancer mortality in patients with schizophrenia: an 11-year prospective cohort study. *Cancer* 2009; 115(15): 3555–3562.
20. Gupta SK, Lamont EB. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. *J Am Geriatr Soc* 2004; 52(10): 1681–1687.
21. Sternbach H. Are antidepressants carcinogenic? A review of preclinical and clinical studies. *J Clin Psychiatry* 2003; 64(10): 1153–1162.
22. Coogan PF, Palmer JR, Strom BL et al Use of selective serotonin reuptake inhibitors and the risk of breast cancer. *Am J Epidemiol* 2005; 162(9): 835–838.
23. Toh S, Rodriguez LAG, Hernandez-Diaz S. Use of antidepressants and risk of lung cancer. *Cancer Causes Control* 2007; 18(10): 1055–1064.
24. Chubak J, Boudreau DM, Rulyak SJ et al Colorectal cancer risk in relation to antidepressant medication use. *Int J Cancer* 2011; 128(1): 227–232.
25. Xu W, Tamim H, Shapiro S et al Use of antidepressants and risk of colorectal cancer: a nested case-control study. *Lancet Oncol* 2006; 7(4): 301–308.
26. Aggarwal A, Freund K, Sato A et al Are depressive symptoms associated with cancer screening and cancer stage at diagnosis among postmenopausal women? The Women's Health Initiative observational cohort. *J Womens Health (Larchmt)* 2008; 17(8): 1353–1361.
27. Chang CK, Hayes RD, Perera G et al Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. *PLoS ONE* 2011; 6(5): e19590.

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Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA)

A. Schneeweiss^{1*}, S. Chia², T. Hickish³, V. Harvey⁴, A. Eniu⁵, R. Hegg⁶, C. Tausch⁷, J. H. Seo⁸, Y.-F. Tsai⁹, J. Ratnayake¹⁰, V. McNally¹⁰, G. Ross¹⁰ & J. Cortés¹¹

¹National Center for Tumor Diseases, University Hospital, Heidelberg, Germany; ²British Columbia Cancer Agency – Vancouver Centre, University of British Columbia, Vancouver, Canada; ³Royal Bournemouth Hospital, Bournemouth University, Bournemouth, UK; ⁴Regional Cancer and Blood Centre, Auckland City Hospital, Auckland, New Zealand; ⁵Cancer Institute "I Chiricuta", Cluj-Napoca, Romania; ⁶Hospital Pérola Byington and FMUSP, São Paulo, Brazil; ⁷Breast Center, Zürich, Switzerland; ⁸Division of Medical Oncology, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea; ⁹Taipei-Veterans General Hospital, Taipei, Taiwan; ¹⁰Roche Products Limited, Welwyn, UK; ¹¹Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

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Background: Pertuzumab (P) combined with trastuzumab (H)-based chemotherapy improves efficacy in early and advanced HER2-positive breast cancer. We assessed the tolerability, with particular focus on cardiac safety, of H and P with chemotherapy in the neoadjuvant treatment of HER2-positive early breast cancer.

*Correspondence to: Dr Andreas Schneeweiss, Head of Division Gynecological Oncology, National Center for Tumor Diseases, University Hospital, Im Neuenheimer Feld 460, 69120 Heidelberg, Germany. Tel: +49-6221-5636051; Fax: +49-6221-567920; E-mail: andreas.schneeweiss@med.uni-heidelberg.de

Patients and methods: In this multicenter, open-label phase II study, patients with operable, locally advanced, or inflammatory breast cancer were randomized 1 : 1 : 1 to receive six neoadjuvant cycles q3w (Arm A: 5-fluorouracil, epirubicin, cyclophosphamide [FEC] + H + P \times 3 \rightarrow docetaxel [T] + H + P \times 3; Arm B: FEC \times 3 \rightarrow T + H + P \times 3; Arm C: T + carboplatin + H [TCH]+P \times 6). pCR was assessed at surgery and adjuvant therapy given to complete 1 year of H.

Results: Two hundred twenty-five patients were randomized. During neoadjuvant treatment, two patients (2.7%; Arm B) experienced symptomatic left ventricular systolic dysfunction (LVSD) and 11 patients (Arm A: 4 [5.6%]; Arm B: 4 [5.3%]; Arm C: 3 [3.9%]) had declines in left ventricular ejection fraction of \geq 10% points from baseline to $<$ 50%. Diarrhea was the most common adverse event. pCR (ypT0/is) was reported for 61.6% (Arm A), 57.3% (Arm B), and 66.2% (Arm C) of patients.

Conclusion: The combination of P with H and standard chemotherapy resulted in low rates of symptomatic LVSD.

Key words: early breast cancer, HER2, LVSD, neoadjuvant, pertuzumab, trastuzumab

introduction

The combination of trastuzumab with pertuzumab, a humanized monoclonal antibody targeting a different epitope of HER2 from trastuzumab, was first studied in patients with HER2-positive metastatic breast cancer whose disease had progressed during previous therapy including trastuzumab [1, 2]. Adverse events were mostly mild or moderate in intensity, and the combination of both antibodies was well tolerated with respect to cardiac safety, with mean left ventricular ejection fraction (LVEF) remaining close to baseline throughout the treatment period [1]. Objective response was reported in 24.2% of patients and a further 25.8% experienced stable disease [1]. These results provided the rationale for studying pertuzumab combined with trastuzumab and chemotherapy in the early disease stages. A neoadjuvant study in patients with HER2-positive early breast cancer showed that the combination of pertuzumab with trastuzumab-based therapy significantly improves pathological complete response (pCR) rate compared with trastuzumab-based therapy alone [3]. Similarly, neoadjuvant studies with trastuzumab and lapatinib showed that the combination of both targeted agents is superior to either agent alone plus chemotherapy [4–6].

HER signaling is involved in myocardial homeostasis and treatment with trastuzumab has been associated with cardiac dysfunction, especially when combined with higher cumulative doses of anthracyclines [7, 8]. The long-term follow-up assessment of cardiac function in an adjuvant study with anthracycline-based chemotherapy and trastuzumab showed an increased incidence of cardiac adverse events in the combination arm; however, the overall risk-benefit assessment favored the combination with trastuzumab [9]. Combined targeting of HER2 by trastuzumab and pertuzumab provides superior efficacy [3, 10]; the investigation of their cardiac tolerability is, however, important, especially when given in combination with anthracyclines for the treatment of HER2-positive breast cancer. The neoadjuvant setting is well suited for drug evaluation, as results provide an early indication not only of the safety profile but equally of their activity in a relatively short period of time, with pCR serving as a surrogate for long-term treatment outcome [11, 12].

TRYPHAENA was undertaken to evaluate the cardiac tolerability of neoadjuvant pertuzumab and trastuzumab given with anthracycline-containing or anthracycline-free standard

chemotherapy regimens in operable, locally advanced or inflammatory HER2-positive breast cancer.

patients and methods

study design

TRYPHAENA (NCT00976989) was a randomized, multicenter, open-label phase II study designed to evaluate the tolerability and activity associated with trastuzumab (Herceptin, F. Hoffmann-La Roche, Ltd; Genentech, Inc.) and pertuzumab (Perjeta, F. Hoffmann-La Roche, Ltd; Genentech, Inc.) in combination with anthracycline- or carboplatin-based neoadjuvant systemic chemotherapy in patients with HER2-positive primary breast cancer. The study was conducted in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each participant. Approval for the protocol and for any modifications was obtained from independent ethics committees.

Patients were randomly allocated to receive neoadjuvant therapy in Arm A: 5-fluorouracil, epirubicin, cyclophosphamide (FEC) followed by docetaxel (T), with trastuzumab (H) and pertuzumab (P) given concurrently throughout (FEC + H + P \times 3 \rightarrow T + H + P \times 3); Arm B: FEC followed by T + H + P (FEC \times 3 \rightarrow T + H + P \times 3); or Arm C: T, carboplatin, H with P (TCH+P \times 6). Following neoadjuvant therapy, patients underwent surgery and continued trastuzumab to complete 1 year of treatment. They received further adjuvant treatment (radiotherapy, chemotherapy, hormonal treatment) according to local guidelines.

The primary objective was to evaluate safety and tolerability during neoadjuvant treatment. Primary safety end points were incidence of symptomatic left ventricular systolic dysfunction (LVSD) as assessed by the investigator, and decline in LVEF of \geq 10% points from baseline to $<$ 50% over the course of neoadjuvant treatment. Secondary objectives assessed activity and safety during neoadjuvant and adjuvant treatment. pCR in the breast was assessed locally, and defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumor at surgery following primary systemic therapy (ypT0/is). Additional secondary end points were clinical response rate, time to clinical response, rate of breast-conserving surgery for patients for whom mastectomy was planned before treatment (T2–3), disease-free survival, progression-free survival, and overall survival. Clinical response rate was defined as the proportion of patients who achieved a complete or partial response at any time before surgery. Tumor response was identified as per local practice. Samples for biomarker analyses were collected.

patients

Female patients aged \geq 18 years with operable (T2-3, N0-1, M0), locally advanced (T2-3, N2 or N3, M0; T4a-c, any N, M0), or inflammatory (T4d,

any N, M0) breast cancer and a primary tumor size >2 cm were eligible. Positive HER2 status by immunohistochemistry (IHC 3+) or by fluorescence *in situ* hybridization (FISH) was centrally confirmed (FISH positivity was mandatory for IHC 2+ tumors). Additional inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and LVEF $\geq 55\%$ at baseline. Exclusion criteria included metastatic disease (stage IV) or bilateral breast cancer; previous systemic or local anticancer therapy; other malignancy, except for carcinoma *in situ* of the cervix, basal cell carcinoma, or squamous cell carcinoma of the skin; inadequate bone marrow, liver, or renal function; uncontrolled hypertension; or history of myocardial infarction within 6 months of enrollment.

Patients were centrally randomized 1 : 1 : 1 via an interactive voice response system. Treatment allocation was dynamic and stratified by operable, locally advanced, and inflammatory breast cancer and by hormone receptor positivity.

treatment

Study drugs were administered intravenously on a 3-weekly schedule and given consecutively on the same day in the following sequence: trastuzumab, followed by pertuzumab, FEC, carboplatin, and docetaxel. Trastuzumab was given at an initial dose of 8 mg/kg, followed by 6 mg/kg; pertuzumab was given at an initial dose of 840 mg, followed by 420 mg. In Arms A and B, the doses administered were 5-fluorouracil: 500 mg/m²; epirubicin: 100 mg/m²; cyclophosphamide: 600 mg/m²; docetaxel: 75 mg/m², escalating to 100 mg/m² if no dose-limiting toxic effect occurred during cycle 4. In Arm C, carboplatin was administered at a dose of AUC6 (area under the plasma concentration-time curve) and docetaxel was given at 75 mg/m² (no dose escalation allowed). Dose modifications for trastuzumab and pertuzumab were not permitted. Docetaxel dose reductions to 75 mg/m² then to 60 mg/m² were allowed; re-escalation was not permitted. Dose reductions of FEC and carboplatin were allowed as per local prescribing information.

assessments

Tumor assessments at baseline, after completion of cycle 6 before surgery, and at the final visit or withdrawal were carried out by mammogram or magnetic resonance imaging (MRI) and clinical breast examination (CBE). During every cycle and at the final visit or withdrawal, tumor response was measured using CBE and/or mammography or other conventional methods as per local practice, such as ultrasound, computed tomography, X-rays, or MRI. LVEF was measured by echocardiography or multiple-gated acquisition, and the same method was to be used for an individual patient throughout the study. LVEF assessments (local and central) were carried out at baseline, during cycles 2, 4, and 6, before cycle 7, during cycles 10, 12, 15, and 18 (Arm B only), and at the final visit or withdrawal. During follow-up, LVEF assessments took place every 6 months for 2 years, then annually for a further 2 years. Adverse events were monitored continuously and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Symptomatic LVSD was reported as a serious adverse event (SAE).

statistical analysis

If the true underlying incidence of symptomatic LVSD in a treatment arm was 3%, the probability of observing more than five such events in that arm was calculated to be 0.025. Ninety-five percent confidence intervals (95% CIs) were calculated for the incidence of symptomatic LVSD and the incidence of LVEF decline by $\geq 10\%$ points from baseline to $<50\%$. pCR (ypT0/is) rates were expected to be $\sim 50\%$ (Arm A), 45% (Arm B), and 40% (Arm C). With 225 patients and if these pCR rates were observed, the minimum true efficacy (lower bound of exact 95% CI) of the estimates was calculated to be 38.9% (Arm A), 33.8% (Arm B), and 28.9% (Arm C). No

formal hypothesis testing was carried out, and no statistical comparisons were made between arms; secondary efficacy end points were calculated and summarized for descriptive purposes only.

results

Between December 2009 and January 2011, 225 patients were recruited from 44 centers in 19 countries; 73 patients were randomized to Arm A, 75 to Arm B, and 77 to Arm C (supplementary Figure S1, available at *Annals of Oncology* online). At data cutoff in July 2012, all patients had completed neoadjuvant and adjuvant treatment and therefore, 1 year of trastuzumab therapy. The median overall time on study including the post-treatment follow-up ranged from 20 to 21 months between arms. Baseline demographics were generally balanced across arms (supplementary Table S2, available at *Annals of Oncology* online), with the exception that more white patients were randomized to Arm C. The proportion of patients with operable breast cancer was lower in Arm C. Correspondingly, more patients in Arm C presented with locally advanced disease. In comparison, more patients in Arm B presented with hormone receptor-negative tumors, and the proportion of patients with HER2 IHC 2+ tumors was higher in Arm A. Potential cardiac risk factors and cardiac medication, excluding medication for adverse events, are presented in supplementary Tables S3 and S4, available at *Annals of Oncology* online. The TNM classification by disease type is presented in supplementary Table S5, available at *Annals of Oncology* online. The majority of patients received all scheduled cycles of neoadjuvant treatment (Arm A: 95.8%, Arm B: 88.0%, Arm C: 92.1%). supplementary Table S6, available at *Annals of Oncology* online presents the study treatment dose received during neoadjuvant therapy.

cardiac tolerability

The incidence of symptomatic LVSD and significant declines in LVEF ($\geq 10\%$ points from baseline to $<50\%$) was low across all arms (Table 1). Two patients (2.7%) in Arm B experienced symptomatic LVSD (dyspnea on exertion) during neoadjuvant treatment. One of these patients experienced the event during FEC-only treatment; therefore, only 1 of 223 patients (0.4%) who received trastuzumab and pertuzumab in combination with standard chemotherapy developed symptomatic LVSD during the neoadjuvant treatment period. Both events resolved after study treatment discontinuation and medication for the event. In the adjuvant period, one patient (1.5%) in Arm C, who received trastuzumab-only treatment, experienced symptomatic LVSD. The patient received medication for the event, and it had resolved 24 days after onset. During the follow-up period, one patient (1.3%) in Arm B experienced symptomatic LVSD (dyspnea on exertion and fatigue). This patient had withdrawn from study after receiving four cycles of neoadjuvant treatment due to pneumonitis. The symptomatic LVSD was considered related to off-study adjuvant trastuzumab treatment. The patient permanently discontinued off-study trastuzumab treatment and received medication for the event. Subsequently, the patient withdrew consent and provided no further details.

Table 1. Cardiac tolerability during the entire study period in the safety population

	FEC + H + P ×3 → T + H + P ×3	FEC ×3 → T + H + P ×3	TCH + P ×6
Neoadjuvant treatment period, <i>n</i>	72	75	76
LVSD (all grades), <i>n</i> (%) 95% CI (%)	4 (5.6) 1.5–13.6	3 (4.0) 0.8–11.2	2 (2.6) 0.3–9.2
Symptomatic LVSD (grade ≥3, SAE), <i>n</i> (%) 95% CI (%)	0 (0.0) 0.0–5.0	2 (2.7) 0.3–9.3	0 (0.0) 0.0–4.7
LVEF decline ≥10% points from baseline to <50%, <i>n</i> (%) 95% CI (%)	4 (5.6) 1.5–13.6	4 (5.3) 1.5–13.1	3 (3.9) 0.8–11.1
Adjuvant treatment period, <i>n</i>	68	65	67
LVSD (all grades), <i>n</i> (%) 95% CI (%)	4 (5.9) 1.6–14.4	5 (7.7) 2.5–17.0	3 (4.5) 0.9–12.5
Symptomatic LVSD (grade ≥3, SAE), <i>n</i> (%) 95% CI (%)	0 (0.0) 0.0–5.3	0 (0.0) 0.0–5.5	1 (1.5) 0.0–8.0
LVEF decline ≥10% points from baseline to <50%, <i>n</i> (%) 95% CI (%)	4 (5.9) 1.6–14.4	8 (12.3) 5.5–22.8	3 (4.5) 0.9–12.5
Follow-up period, <i>n</i>	70	75	74
LVSD (all grades), <i>n</i> (%) 95% CI (%)	1 (1.4) 0.0–7.7	2 (2.7) 0.3–9.3	1 (1.4) 0.0–7.3
Symptomatic LVSD (grade ≥3, SAE), <i>n</i> (%) 95% CI (%)	0 (0.0) 0.0–5.1	1 (1.3) 0.0–7.2	0 (0.0) 0.0–4.9
LVEF decline ≥10% points from baseline to <50%, <i>n</i> (%) 95% CI (%)	3 (4.3) 0.9–12.0	4 (5.3) 1.5–13.1	2 (2.7) 0.3–9.4

CI, confidence interval; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; SAE, serious adverse event. FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel, carboplatin, trastuzumab.

During neoadjuvant treatment, four patients (5.6%) in Arm A, four (5.3%) in Arm B, and three (3.9%) in Arm C experienced LVEF declines of ≥10% points from baseline to <50%. Measurements had improved to ≥50% in all patients at data cutoff. Fifteen patients (four [5.9%] in Arm A, eight [12.3%] in Arm B, and three [4.5%] in Arm C) had significant declines in LVEF during adjuvant treatment; all of these declines had improved to ≥50% at data cutoff. During follow-up, nine patients (three [4.3%] in Arm A, four [5.3%] in Arm B, and two [2.7%] in Arm C) experienced significant LVEF declines; LVEF values had improved to ≥50% in three of nine patients at data cutoff. Following the data cutoff in July 2012, LVEF values recovered to ≥50% in all remaining patients; the only exception was one patient in Arm B who withdrew consent and no further follow-up data could be collected. Overall, 24 patients experienced significant LVEF declines during the study. The declines were asymptomatic in 21 of these patients.

Mean LVEF dropped below baseline during the treatment period in all arms; however, mean decreases were no more than

7% points based on central readings (Figure 1). The profiles of LVEF changes over time were similar between arms.

safety profile

During the neoadjuvant treatment period, diarrhea, alopecia, and nausea (all grades) were reported in >50% of patients across all arms (Table 2). Neutropenia, febrile neutropenia, and leukopenia were the most frequently reported grade ≥3 adverse events (Table 2). The incidence of SAEs was highest in Arm C (35.5%), followed by Arm A (27.8%) and Arm B (20.0%). The most common SAE was febrile neutropenia (Arm A: 13.9%, Arm B: 5.3%, Arm C: 14.5%). Neutropenia was reported as an SAE in 2.8% (Arm A), 4.0% (Arm B), and 1.3% (Arm C) of patients; diarrhea was reported as an SAE in 1.4% (Arm A), 4.0% (Arm B), and 5.3% (Arm C) of patients. All other SAEs occurred in ≤2 patients in any arm.

During adjuvant treatment, radiation skin injury and arthralgia were the most frequently reported adverse events (all grades), reported in >10% of patients (Table 2). Adverse events of grade ≥3 were rare during adjuvant treatment with

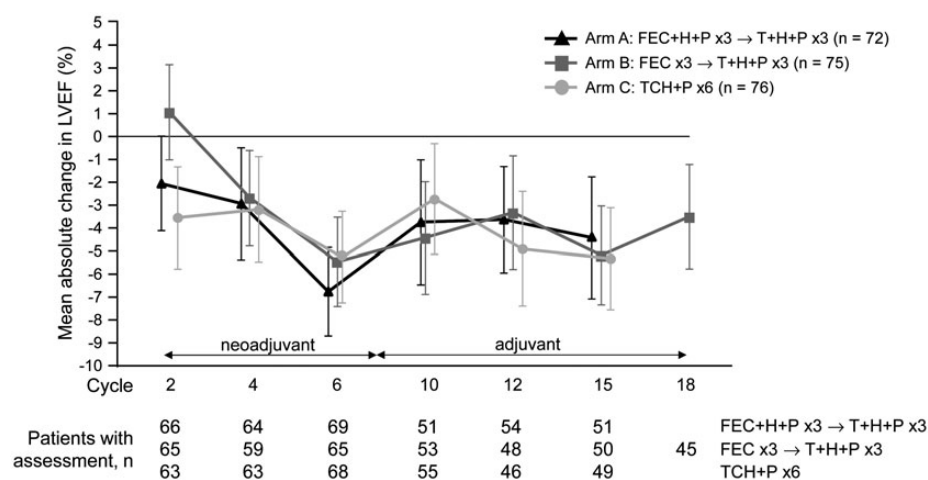


Figure 1. Mean change in LVEF from baseline during the treatment period by central readings. Shown is the mean change in LVEF from baseline during the neoadjuvant and adjuvant treatment periods in the safety population according to study treatment received. LVEF, left ventricular ejection fraction; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel, carboplatin, trastuzumab.

Table 2. Adverse events (all grades and grade ≥ 3) during the neoadjuvant and adjuvant treatment periods in the safety population

	FEC + H + P $\times 3 \rightarrow$ T + H + P $\times 3$	FEC $\times 3 \rightarrow$ T + H + P $\times 3$	TCH + P $\times 6$
Neoadjuvant treatment period, <i>n</i>	72	75	76
10 most common adverse events (all grades), <i>n</i> (%)			
Diarrhea	44 (61.1)	46 (61.3)	55 (72.4)
Alopecia	35 (48.6)	39 (52.0)	41 (53.9)
Nausea	38 (52.8)	40 (53.3)	34 (44.7)
Neutropenia	37 (51.4)	35 (46.7)	37 (48.7)
Vomiting	29 (40.3)	27 (36.0)	30 (39.5)
Fatigue	26 (36.1)	27 (36.0)	32 (42.1)
Anemia	14 (19.4)	6 (8.0)	28 (36.8)
Mucosal inflammation	17 (23.6)	15 (20.0)	13 (17.1)
Constipation	13 (18.1)	17 (22.7)	12 (15.8)
Dyspepsia	18 (25.0)	6 (8.0)	17 (22.4)
10 most common adverse events (grade ≥ 3), <i>n</i> (%)			
Neutropenia	34 (47.2)	32 (42.7)	35 (46.1)
Febrile neutropenia	13 (18.1)	7 (9.3)	13 (17.1)
Leukopenia	14 (19.4)	9 (12.0)	9 (11.8)
Diarrhea	3 (4.2)	4 (5.3)	9 (11.8)
Anemia	1 (1.4)	2 (2.7)	13 (17.1)
Thrombocytopenia	0 (0.0)	0 (0.0)	9 (11.8)
Vomiting	0 (0.0)	2 (2.7)	4 (5.3)
Drug hypersensitivity	2 (2.8)	0 (0.0)	2 (2.6)
Fatigue	0 (0.0)	0 (0.0)	3 (3.9)
Alanine aminotransferase increase	0 (0.0)	0 (0.0)	3 (3.9)
Adjuvant treatment period, <i>n</i>	68	65	67
10 most common adverse events (all grades), <i>n</i> (%)			
Radiation skin injury	11 (16.2)	14 (21.5)	7 (10.4)
Arthralgia	11 (16.2)	12 (18.5)	6 (9.0)
Hot flushes	9 (13.2)	6 (9.2)	4 (6.0)
Diarrhea	7 (10.3)	5 (7.7)	6 (9.0)
Headache	9 (13.2)	5 (7.7)	3 (4.5)
Fatigue	6 (8.8)	4 (6.2)	5 (7.5)
Musculoskeletal chest pain	5 (7.4)	3 (4.6)	5 (7.5)
Musculoskeletal pain	6 (8.8)	5 (7.7)	2 (3.0)
Erythema	5 (7.4)	2 (3.1)	6 (9.0)
Edema peripheral	6 (8.8)	3 (4.6)	4 (6.0)
Myalgia	3 (4.4)	10 (15.4)	0 (0.0)
Adverse events (grade ≥ 3) in >1 patient overall, <i>n</i> (%)			
Neutropenia	3 (4.4)	3 (4.6)	1 (1.5)
Pneumonia	2 (2.9)	0 (0.0)	0 (0.0)
Erythema	2 (2.9)	0 (0.0)	0 (0.0)

FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel, carboplatin, trastuzumab.

neutropenia being most common. All SAEs reported during adjuvant treatment occurred in ≤ 2 patients in any arm.

No death was reported during neoadjuvant treatment. During adjuvant treatment, one patient in Arm A presented with malignant neoplasm and withdrew from study treatment. This disease progression was reported as an adverse event, and the patient died on study day 337 during follow-up. An additional

five deaths during follow-up were due to disease recurrence (Arm A: 1, Arm B: 2, Arm C: 2).

efficacy

The majority of patients achieved a pCR in the breast (ypT0/is): 61.6% (Arm A), 57.3% (Arm B), and 66.2% (Arm C) (Figure 2). The pCR rate was higher in patients with hormone receptor-negative tumors compared with patients with hormone receptor-positive tumors. When pCR was defined as ypT0 ypN0, 50.7% (Arm A), 45.3% (Arm B), and 51.9% (Arm C) of patients achieved a pCR.

Objective response was reported in 89.6%–94.7% of patients (supplementary Table S7, available at *Annals of Oncology* online). Clinical complete response was achieved by 50.7% of patients in Arm A, 28.0% in Arm B, and 40.3% in Arm C. One patient in Arm B experienced disease progression during neoadjuvant treatment. This patient had presented with locally advanced disease at baseline and received one cycle of FEC before disease progression was diagnosed.

Mastectomy was planned for 46, 36, and 37 patients in Arms A, B, and C, respectively. Among these patients, 21.7% (Arm A), 16.7% (Arm B), and 27.0% (Arm C) were able to undergo breast-conserving surgery following neoadjuvant systemic therapy.

discussion

The main objective of TRYPHAENA was to evaluate the tolerability, particularly with respect to cardiac function, of three neoadjuvant treatment regimens combining pertuzumab with trastuzumab and either a standard anthracycline- or platinum-based chemotherapy for the treatment of primary HER2-positive breast cancer. The combination of trastuzumab and pertuzumab was generally well tolerated regardless of whether it was given sequentially or concomitantly with anthracycline-based, or combined with carboplatin-based, chemotherapy. The study was not intended to evaluate superiority of any arm, and all three arms were experimental. Therefore, comparison of toxic effect and response rates with a control arm is not possible which limits the interpretation of the study. Nevertheless, the response rates achieved with each regimen are encouraging, with pCR rates of 57%–66%.

Owing to the different patient populations, treatment settings and durations, therapies administered, and follow-up periods, the comparison of results from different trials is controversial. However, results from TRYPHAENA and previous studies [8, 13–16] provide a context from which it appears that pertuzumab does not increase the rate of cardiac dysfunction observed in combinations of trastuzumab plus standard chemotherapy. These observations are supported by a meta-analysis of patients treated with pertuzumab or trastuzumab [17]. The recently reported findings in a randomized, placebo-controlled phase III study conducted in first-line HER2-positive metastatic breast cancer, CLEOPATRA, provide strong evidence that pertuzumab does not affect cardiac disorders or cardiac function parameters, particularly LVSD and LVEF [18].

Assessment of pCR (ypT0/is) showed that all three treatment regimens were highly active, with pCR rates between 57.3% and 66.2% following 18 weeks of neoadjuvant therapy. The majority of patients achieved a partial response resulting in the high

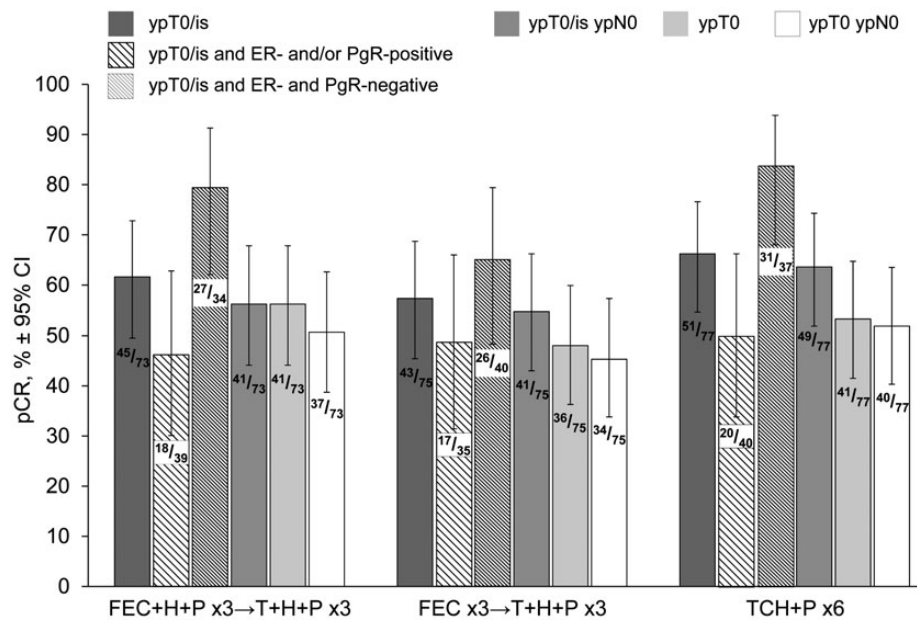


Figure 2. Pathological complete response in the ITT population. pCR rates and their respective 95% CIs are shown for pCR defined as ypT0/is, ypT0/is ypN0, ypT0, and ypT0 ypN0. pCR rates according to ypT0/is are also presented for patients with ER- and/or PgR-positive tumors and patients with ER- and PgR-negative tumors. Exact numbers of patients achieving pCR (*n/N*) are displayed within the bars. ypT0/is, no invasive tumor residues in the breast, DCIS/LCIS in the breast at surgery allowed; ypT0/is ypN0, no invasive tumor residues in the breast and lymph nodes, DCIS/LCIS in the breast at surgery allowed; ypT0, no invasive and noninvasive tumor residues in the breast at surgery; ypT0 ypN0, no invasive and noninvasive tumor residues in the breast and lymph nodes at surgery. CI, confidence interval; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; ITT, intent-to-treat; LCIS, lobular carcinoma *in situ*; pCR, pathological complete response; PgR, progesterone receptor. FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel, carboplatin, trastuzumab.

objective response rate of 89.6%–94.7%. In comparison with this study, a previous neoadjuvant study (NOAH) with trastuzumab-based chemotherapy resulted in a pCR rate of 42.7% following 33 weeks of treatment [15]. Several neoadjuvant studies suggest that the combination of two agents targeting the HER family results in superior pCR rates compared with either agent alone. NeoSphere combined pertuzumab with trastuzumab plus docetaxel for 12 weeks of neoadjuvant therapy resulting in a pCR rate of 45.8% [3]. The NeoALTTO, CHER-LOB, and NSABP B-41 trials combined trastuzumab with lapatinib for 18, 26, and 28 weeks of neoadjuvant treatment, respectively, resulting in pCR rates of 51.3% [4], 46.7% [5], and 62.0% [6].

Overall, our data show that neoadjuvant pertuzumab and trastuzumab, given concurrently or sequentially with an anthracycline-based, or concurrently with a carboplatin-based chemotherapy regimen, result in a low incidence of LVSD. Together with the significantly improved pCR rate reported for the combination of pertuzumab with trastuzumab and docetaxel in NeoSphere [3], these results are encouraging with regard to an ongoing phase III study of trastuzumab and pertuzumab with standard chemotherapy regimens in the adjuvant setting in patients with HER2-positive early breast cancer (APHINITY; NCT01358877).

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disclosure

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references

1. Baselga J, Gelmon KA, Verma S et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive

- metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol* 2010; 28: 1138–1144.
2. Cortés J, Fumoleau P, Bianchi GV et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2012; 30: 1594–1600.
 3. Gianni L, Pienkowski T, Im YH et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; 13: 25–32.
 4. Baselga J, Bradbury I, Eidtmann H et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2012; 379: 633–640.
 5. Guarneri V, Frassoldati A, Bottini A et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. *J Clin Oncol* 2012; 30: 1989–1995.
 6. Robidoux A, Tang G, Rastogi P et al. Evaluation of lapatinib as a component of neoadjuvant therapy for HER2+ operable breast cancer: NSABP protocol B-41. *J Clin Oncol* 2012; 30(18 Suppl): Abstract LBA506.
 7. Seidman A, Hudis C, Pierri MK et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; 20: 1215–1221.
 8. Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365: 1273–1283.
 9. Romond EH, Jeong JH, Rastogi P et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2012; 30: 3792–3799.
 10. Baselga J, Cortes J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366: 109–119.
 11. von Minckwitz G, Kaufmann M, Kuemmel S et al. Correlation of various pathologic complete response (pCR) definitions with long-term outcome and prognostic value of pCR in various breast cancer subtypes: results from the German neoadjuvant meta-analysis. *J Clin Oncol* 2011; 29(9 Suppl): Abstract 1028.
 12. Rastogi P, Anderson SJ, Bear HD et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008; 26: 778–785.
 13. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; 353: 1659–1672.
 14. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; 353: 1673–1684.
 15. Gianni L, Eiermann W, Semiglazov V et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet* 2010; 375: 377–384.
 16. Tan-Chiu E, Yothers G, Romond E et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; 23: 7811–7819.
 17. Lenihan D, Suter T, Brammer M et al. Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab. *Ann Oncol* 2012; 23: 791–800.
 18. Swain SM, Ewer MS, Cortés J et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. *Oncologist* 2013; 18: 257–264.

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A prospective, multicenter validation study of a prognostic index composed of S-phase fraction, progesterone receptor status, and tumour size predicts survival in node-negative breast cancer patients: **NNBC**, the node-negative breast cancer trial

M. Klintman^{1,2*}, F. Nilsson³, P.-O. Bendahl¹, M. Fernö¹, G. Liljegren⁴, S. Emdin³, & P. Malmström^{1,2}
For the Swedish Breast Cancer Group

¹Department of Clinical Sciences, Division of Oncology, Lund University, Lund; ²Skåne Department of Oncology, Skåne University Hospital, Lund; ³Department of Clinical Sciences, Division of Surgery, Umeå University and Umeå University Hospital, Umeå; ⁴Department of Clinical Sciences, Division of Surgery, Örebro University Hospital and the Centre for Assessment of Medical Technology (CAMTÖ) in Örebro, Sweden

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Background: In a retrospective study on node-negative breast cancer, a prognostic index consisting of a proliferation factor, S-phase fraction (SPF), progesterone receptor status (PR), and tumour size identified one-third of patients as high

*Correspondence to: Dr Marie Klintman, Department of Clinical Sciences, Division of Oncology, Barngatan 2B, Skåne University Hospital, Lund, SE 221 85 Lund, Sweden.
Tel: +46-461-78554, +46-730-929096; Fax: +46-461-47327; E-mail: marie.klintman@med.lu.se