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

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Summary

Background Studies with pertuzumab, a novel anti-HER2 antibody, show improved efficacy when combined with the established HER2-directed antibody trastuzumab in breast cancer therapy. We investigated the combination of pertuzumab or trastuzumab, or both, with docetaxel and the combination of pertuzumab and trastuzumab without chemotherapy in the neoadjuvant setting.

Methods In this multicentre, open-label, phase 2 study, treatment-naive women with HER2-positive breast cancer were randomly assigned (1:1:1:1) centrally and stratified by operable, locally advanced, and inflammatory breast cancer, and by hormone receptor expression to receive four neoadjuvant cycles of: trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) plus docetaxel (75 mg/m², escalating, if tolerated, to 100 mg/m² every 3 weeks; group A) or pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks) and trastuzumab plus docetaxel (group B) or pertuzumab and trastuzumab (group C) or pertuzumab plus docetaxel (group D). The primary endpoint, examined in the intention-to-treat population, was pathological complete response in the breast. Neither patients nor investigators were masked to treatment. This study is registered with ClinicalTrials.gov, number NCT00545688.

Findings Of 417 eligible patients, 107 were randomly assigned to group A, 107 to group B, 107 to group C, and 96 to group D. Patients given pertuzumab and trastuzumab plus docetaxel (group B) had a significantly improved pathological complete response rate (49 of 107 patients; 45·8% [95% CI 36·1–55·7]) compared with those given trastuzumab plus docetaxel (group A; 31 of 107; 29·0% [20·6–38·5]; p=0·0141). 23 of 96 (24·0% [15·8–33·7]) women given pertuzumab plus docetaxel (group D) had a pathological complete response, as did 18 of 107 (16·8% [10·3–25·3]) given pertuzumab and trastuzumab (group C). The most common adverse events of grade 3 or higher were neutropenia (61 of 107 women in group A, 48 of 107 in group B, one of 108 in group C, and 52 of 94 in group D), febrile neutropenia (eight, nine, none, and seven, respectively), and leucopenia (13, five, none, and seven, respectively). The number of serious adverse events was similar in groups A, B, and D (15–20 serious adverse events per group in 10–17% of patients) but lower in group C (four serious adverse events in 4% of patients).

Interpretation Patients given pertuzumab and trastuzumab plus docetaxel (group B) had a significantly improved pathological complete response rate compared with those given trastuzumab plus docetaxel, without substantial differences in tolerability. Pertuzumab and trastuzumab without chemotherapy eradicated tumours in a proportion of women and showed a favourable safety profile. These findings justify further exploration in adjuvant trials and support the neoadjuvant approach for accelerating drug assessment in early breast cancer.

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Introduction

20–25% of breast cancers overexpress HER2 and are associated with poor prognosis if untreated.[1] Trastuzumab, a HER2-directed humanised monoclonal antibody, combined with chemotherapy, significantly improves response rates, time to progression, and overall survival in women with HER2-positive metastatic breast cancer compared with chemotherapy alone.[2] Furthermore, in women with operable disease, trastuzumab improves disease-free survival and overall survival when given for 1 year in combination with or sequentially after chemotherapy, as recommended for adjuvant therapy with trastuzumab.[3,4] Positive efficacy outcomes with trastuzumab prompted the search to identify other HER2-targeted drugs capable of improving the therapeutic effects of trastuzumab in combination or in sequential administration.[5]

Pertuzumab is an investigational humanised monoclonal antibody directed at the dimerisation domain of HER2.[6] Because of their different bindings sites, trastuzumab and pertuzumab have complementary mechanisms of action. Whereas trastuzumab blocks HER2 cleavage and inhibits ligand-independent signalling,[7] pertuzumab exerts its

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effects by inhibiting ligand-dependent signalling, particularly between HER2 and HER3, which is known to activate a potent cell survival and proliferation signal.[8,9] Both antibodies induce antibody-dependent cell-mediated cytotoxic effects.[10] In a phase 2 trial[11] in patients with HER2-positive metastatic breast cancer, almost a quarter of patients treated with pertuzumab and trastuzumab after tumour progression during previous trastuzumab-based therapy achieved an objective response.

Administration of drug therapy to women with operable or locally advanced breast cancer before surgery (neoadjuvant therapy) has emerged as a successful approach to allow for surgery in cases that are inoperable at diagnosis, or to allow use of breast-sparing approaches rather than mastectomy.[12,13] A corollary aspect of neoadjuvant treatment is the ability to assess antitumour activity of new treatment regimens in terms of pathological findings instead of imaging results or late-emerging evidence such as survival. Based on comparative rates of pathological complete response, neoadjuvant trials are ideally suited to accelerate the assessment of new drugs. Pathological complete response consists of pathological evidence of eradication of invasive cancer after pre-surgery drug administration and serves as a surrogate for long-term efficacy,[12,14,15] providing a robust rationale to design adjuvant trials. Combination of neoadjuvant chemotherapy with trastuzumab has substantially improved rates of pathological complete response.[14,16]

Here, we present the results of the NeoSphere study in which the activity of pertuzumab was assessed by comparing the therapeutic effects of the conventional combination of trastuzumab plus docetaxel with the combination of pertuzumab with either docetaxel or trastuzumab, or both, in a neoadjuvant setting.

Methods

Study design and patients

NeoSphere is a randomised, multicentre, international, open-label phase 2 study in women with locally advanced, inflammatory, or early HER2-positive breast cancer.

All eligible patients had centrally confirmed HER2-positive, operable (T2–3, N0–1, M0), locally advanced (T2–3, N2–3, M0 or T4a–c, any N, M0), or inflammatory (T4d, any N, M0) breast cancer with primary tumours larger than 2 cm in diameter, were aged 18 years or older, and had not received any previous cancer therapy. Tumours had to be HER2 immunohistochemistry 3+ or 2+ and positive for fluorescence or chromogenic in-situ hybridisation. Other main inclusion criteria were: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, baseline left ventricular ejection fraction (LVEF) of 55% or more, as measured by echocardiography or multiple gated acquisition (MUGA). Key exclusion criteria were metastatic disease (stage IV), bilateral breast cancer, other malignancies, inadequate bone marrow or renal function, impaired liver function, impaired cardiac function, uncontrolled hypertension, pregnancy, and refusal to use contraception.

The study was undertaken in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

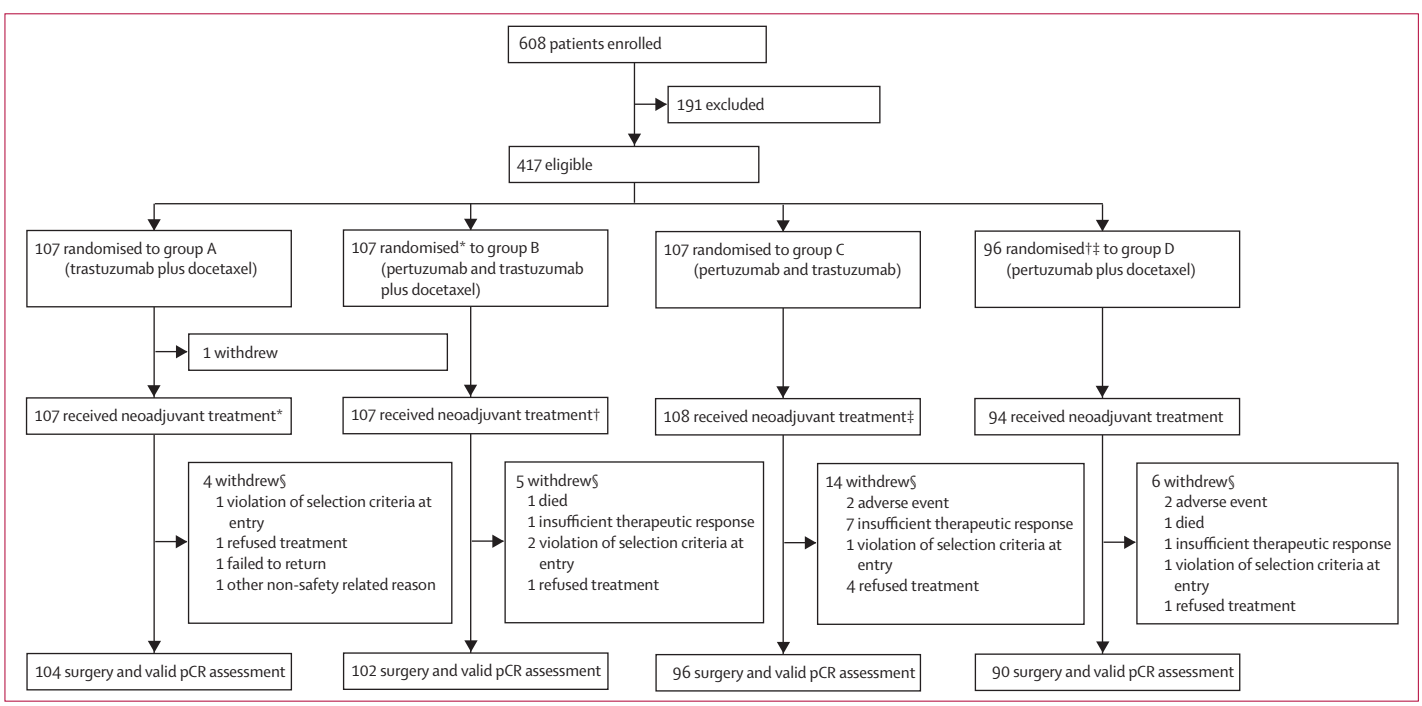

Figure 1: **Trial profile**
pCR=pathological complete response. *One patient randomly assigned to group B received group A treatment. †One patient randomly assigned to group D received group B treatment. ‡One patient randomly assigned to group D received group C treatment. §Indicates withdrawal from neoadjuvant study treatment; patients withdrawing from neoadjuvant treatment could still undergo surgery.

All patients provided written informed consent. Approvals for the study protocol (and any modifications thereof) were obtained from independent ethics committees.

Randomisation and masking

Patients were centrally randomly assigned (1:1:1:1) to receive one of four neoadjuvant treatments: trastuzumab (Roche, Basel, Switzerland) plus docetaxel (Sanofi-Aventis, Paris, France; group A); pertuzumab (Roche, Basel, Switzerland) and trastuzumab plus docetaxel (group B); pertuzumab and trastuzumab without chemotherapy (group C); or pertuzumab plus docetaxel (group D). After 29 patients had been recruited to the study, group D was added to assess the activity of pertuzumab plus docetaxel without trastuzumab.

We used an interactive voice response system to obtain screening information for every patient. Patients were randomly assigned treatment by a central randomisation procedure with the adaptive randomisation method and stratified by operable, locally advanced, and inflammatory breast cancer, and by positivity for oestrogen or progesterone receptors. This trial was open label.

Procedures

Trastuzumab was given every 3 weeks at 8 mg/kg (cycle 1), followed by 6 mg/kg. The pertuzumab loading dose was 840 mg, followed by 420 mg every 3 weeks. Docetaxel was given at 75 mg/m², escalating, if tolerated, to 100 mg/m² every 3 weeks. After completion of neoadjuvant treatment (four intravenous cycles), eligible patients underwent surgery and adjuvant FEC therapy (three cycles of fluorouracil 600 mg/m² intravenously, epirubicin 90 mg/m² intravenously, and cyclophosphamide 600 mg/m² intravenously every 3 weeks) in all groups except for group C, in which patients received four cycles of docetaxel before FEC. All patients received concomitant trastuzumab every 3 weeks for 1 year. Radiotherapy and standard hormone treatment for patients positive for oestrogen receptor were prescribed as per local guidelines.

Tumour response (clinical breast examination) was assessed at every cycle. Patients underwent physical examination, mammogram, and ultrasound (if required by local practice) before breast surgery. Surgical specimens were assessed locally for pathological complete response. Tumour samples for banking were obtained at study entry and at surgery for the assessment of biomarkers that might be predictive of response to pertuzumab and trastuzumab or prognostic for breast cancer. Results of biomarker analyses will be reported separately.

According to protocol, attending doctors were free to decide when a patient was not deriving benefit, to report progression, and to discontinue the allocated protocol treatment irrespective of the Response Evaluation Criteria In Solid Tumors (RECIST) definition of progression.

We measured LVEF by echocardiography (or MUGA) every second cycle and compiled the baseline LVEF value and the maximum absolute change from baseline. We assessed laboratory parameters, blood counts, ECOG status, and vital signs at every cycle and monitored adverse events continuously until 28 days after the last treatment. We graded the intensity of these events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3·0.

The primary endpoint was pathological complete response in the breast, which is defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery. Remaining in-situ lesions were allowed. Pathologists at participating centres followed guidelines for the assessment of pathological complete response on serial sections of the surgical specimen (appendix). Blinded pathology data were reviewed by a consultant pathologist at regular intervals to ensure consistency. Secondary objectives included clinical response rate (derived clinical response according to RECIST version 1·0[17]), time to clinical response, breast-conserving surgery rate, and safety.

See Online for appendix

Statistical analysis

We planned a sample size of 400 patients to provide about 80% power to detect an absolute difference in pathological complete response of 15% between groups. We expected a

	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=107)	Pertuzumab plus docetaxel (group D; n=96)
Median age (years, range)	50 (32–74)	50 (28–77)	49 (22–80)	49 (27–70)
Ethnic origin				
Black	0	2 (2%)	1 (1%)	3 (3%)
White	80 (75%)	77 (72%)	79 (74%)	61 (64%)
Asian	25 (23%)	23 (21%)	22 (21%)	25 (26%)
Other	2 (2%)	5 (5%)	5 (5%)	7 (7%)
ECOG performance status				
0	100 (94%)*	96 (90%)	92 (86%)	80 (83%)
1	6 (6%)*	11 (10%)	15 (14%)	16 (17%)
ER positive or PR positive, or both	50 (47%)	50 (47%)	51 (48%)*	46 (48%)
ER negative and PR negative	57 (53%)	57 (53%)	55 (52%)*	50 (52%)
Operable	64 (60%)	65 (61%)	65 (61%)	60 (63%)
Locally advanced	36 (34%)	32 (30%)	35 (33%)	31 (32%)
Inflammatory	7 (7%)	10 (9%)	7 (7%)	5 (5%)
Lymph node status				
N0	32 (30%)	31 (29%)*	32 (30%)	28 (29%)
N1	48 (45%)	53 (50%)*	46 (43%)	41 (43%)
N2	22 (21%)	22 (21%)*	24 (22%)	22 (23%)
N3	5 (5%)	0	5 (5%)	5 (5%)
Median tumour size (mm) at clinical breast examination (range)	50 (20–200)	55 (20–150)	50 (20–200)	50 (0–180)

Data are number (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. ER=oestrogen receptor. PR=progesterone receptor. *Data missing for one patient.

***Table 1*: Patient demographics at baseline**

	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=107)	Pertuzumab plus docetaxel (group D; n=96)
Pathological complete response in ITT population	31 (29·0%, 20·6–38·5)	49 (45·8%, 36·1–55·7)*	18 (16·8%, 10·3–25·3)†	23 (24·0%, 15·8–33·7)‡
Pathological complete response and N– at surgery	23 (21·5%, 14·1–30·5)	42 (39·3%, 30·0–49·2)	12 (11·2%, 5·9–18·8)	17 (17·7%, 10·7–26·8)
Pathological complete response and N+ at surgery	8 (7·5%, 3·3–14·2)	7 (6·5%, 2·7–13·0)	6 (5·6%, 2·1–11·8)	6 (6·3%, 2·3–13·1)
Pathological complete response in ER positive or PR positive, or both, women	10/50 (20·0%, 10·0–33·7)	13/50 (26·0%, 14·6–40·3)	3/51 (5·9%, 1·2–16·2)	8/46 (17·4%, 7·8–31·4)
Pathological complete response in ER negative and PR negative women	21/57 (36·8%, 24·4–50·7)	36/57 (63·2%, 49·3–75·6)	15/55 (27·3%, 16·1–41·0)	15/50 (30·0%, 17·9–44·6)

Data are n (%, 95% CI) or n/N (%, 95% CI). ITT=intention-to-treat. N–=lymph-node negative. N+=lymph-node positive. ER=oestrogen receptor. PR=progesterone receptor. *p=0·0141 *vs* group A. †p=0·0198 *vs* group A. ‡p=0·003 *vs* group B.

Table 2: **Pathological complete responses in the ITT population, by hormone-receptor status, and by axillary lymph node status at surgery**

	Trastuzumab plus docetaxel (group A)	Pertuzumab, trastuzumab, and docetaxel (group B)	Pertuzumab plus trastuzumab (group C)	Pertuzumab plus docetaxel (group D)
Clinical response in primary breast tumour				
Complete or partial response	79/99 (79·8%, 70·5–87·2)	89/101 (88·1%, 80·2–93·7)	69/102 (67·6%, 57·7–76·6)	65/91 (71·4%, 61·0–80·4)
Non-responders (including unknown)	20/99 (20·2%, 12·8–29·5)	12/101 (11·9%, 6·3–19·8)	33/102 (32·4%, 23·4–42·3)	26/91 (28·6%, 19·6–39·0)
Overall response in all breast tumours and nodes examined				
Complete or partial response	79/97 (81·4%, 72·3–88·6)	88/100 (88·0%, 80·0–93·6)	65/98 (66·3%, 56·1–75·6)	65/88 (73·9%, 63·4–82·7)
Non-responders (including unknown)	18/97 (18·6%, 11·4–27·7)	12/100 (12·0%, 6·4–20·0)	33/98 (33·7%, 24·4–43·9)	23/88 (26·1%, 17·3–36·6)

For clinical response, data are n/number with clinical breast examination (%, 95% CI); for overall response, data are n/number with clinical breast examination of sum total of breast tumours and all nodes examined (%, 95% CI). 95% CI for one sample binomial with Pearson-Clopper method.

Table 3: **Clinical responses by clinical breast examination during neoadjuvant treatment**

pathological complete response rate of 25% in group A and group D and a rate of 40% in group B or group C. We present intention-to-treat analyses unless otherwise specified. We planned three comparisons (group A *vs* B, group A *vs* C, and group B *vs* D) using a two-sided Cochrane Mantel-Haenszel test at an alpha level of 0·2 (SAS version 8.2). We used breast cancer status and hormone receptor status at baseline as stratification factors. Formal comparison of group D with group A was not prespecified because group D was added to the study after a protocol amendment and, hence, was not powered to test hypotheses.

This is a phase 2, proof-of-concept study and, therefore, the main focus was to make preliminary estimates of the level of activity associated with the experimental treatment groups. Therefore, the α level was set at a 20% level rather than a 5% level as conventionally used in confirmatory trials. The data cutoff for this primary study report of the neoadjuvant phase of the trial occurred at the last patient's surgery or withdrawal in December, 2009. This study is registered with ClinicalTrials.gov, number NCT00545688.

Role of the funding source

The study was conceived and designed by LG and the Fondazione Michelangelo and was done and analysed in collaboration with F Hoffmann-La Roche. F Hoffmann-La Roche funded the study, provided study drugs, and was involved in study design, protocol development, regulatory and ethics approvals, safety monitoring and reporting, data management, and data analysis. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were enrolled across 59 centres in 16 countries from Dec 17, 2007, to Dec 22, 2009. Figure 1 shows patient disposition. Of 417 eligible patients, 392 underwent surgery as planned, and all those who did so had a valid assessment of pathological response. Baseline characteristics were balanced across treatment groups (table 1). The baseline median tumour size at clinical breast examination was at least 50 mm across all groups of the study (table 1). The median docetaxel dose intensity was very close to the maximum planned dose intensity of 31·25 mg/m² per week in all groups of patients (appendix).

A pathological complete response was noted in 31 of 107 women (29·0%, 95% CI 20·6–38·5) given trastuzumab plus docetaxel (group A) compared with 49 of 107 (45·8%, 36·1–55·7) given pertuzumab, trastuzumab, and docetaxel (group B; table 2; p=0·0141). By comparison, 23 of 96 women (24·0%, 15·8–33·7) given pertuzumab plus docetaxel (group D) had a pathological complete response, as did 18 of 107 (16·8%, 10·3–25·3) women treated with both anti-HER2 antibodies but without chemotherapy (group C; table 2).

Consistent with findings in previous studies,[14] fewer pathological complete responses were noted in tumours that were hormone receptor-positive (table 2). In patients with hormone receptor-negative tumours, pathological complete responses were noted in 36 of 57 women (63·2%)

who received both anti-HER2 antibodies and chemotherapy (group B; table 2). In group C (without chemotherapy), 15 of 55 (27·3%) patients with hormone receptor-negative tumours had complete eradication of the tumour in the breast, which was a greater proportion than that achieved in patients with hormone receptor-positive tumours in all groups (table 2). The proportion of patients who were lymph node-negative at surgery and achieved pathological complete response in the breast was highest in group B (table 2). The number of dissected and positive lymph nodes at surgery is shown in the appendix.

Most patients achieved an objective response (complete response or partial response) in the primary lesion (table 3). As noted for pathological complete responses, the greatest clinical response was reported in group B (table 3). Few patients had insufficient therapeutic response (as per investigators' decision) during the neoadjuvant treatment period, although numbers were higher in group C where patients received both anti-HER2 antibodies without chemotherapy (no patients in group A, one [0·9%] patient in group B, seven [6·5%] in group C, and one [1·0%] in group D).

The most frequently occurring adverse events were alopecia, neutropenia, diarrhoea, nausea, fatigue, rash, and mucosal inflammation (table 4). Most adverse events were of grades 1–2. Nearly all of the most frequent adverse events were deemed possibly related to study treatment. The most common adverse events of grade 3 or higher were neutropenia, febrile neutropenia, and leucopenia, as expected for treatment with docetaxel (table 5). The incidence of febrile neutropenia was 7–8% in groups A, B, and D; no patient had febrile neutropenia in group C (without chemotherapy). The overall incidence of adverse events of grade 3 or higher was lowest in group C (eight [2%] of 326 events), in which no chemotherapy was given and ranged from 12% (97 of 803 events; group B) to 14% (110 of 806 events; group A) in the other three treatment groups.

The number of serious adverse events was similar in groups A, B, and D (15–20 serious adverse events per group in 10–17% of patients), but lower in group C (four serious adverse events in 4% of patients; table 5). Neutropenia and febrile neutropenia were the most frequent serious adverse events. Two patients died during the neoadjuvant phase (table 5). One death was caused by fulminant hepatitis possibly related to treatment, which began after treatment cycle 4 in group B. This patient had a high body-mass index, hypertension, and type 2 diabetes. The other death occurred in group D; this patient died of lung metastases and progressive disease. The possible presence of lung metastases was not evident at randomisation.

Figure 2 shows the relative LVEF changes from baseline in the four groups of the study. The mean maximum decrease in LVEF measurement was low (4–5%) and was balanced across treatment groups. No significant change was detected when pertuzumab was added to trastuzumab and no patient had an LVEF decrease to less than 40% at any time during the study. Four patients (one in group A and three in group B) showed LVEF declines of 10–15% from baseline and to less than 50% during the neoadjuvant period. One patient in group C and one in group D had decreases of at least 15% from baseline to less than 50%.

	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=108)	Pertuzumab plus docetaxel (group D; n=94)
Alopecia	70 (65%)	68 (64%)	1 (1%)	63 (67%)
Neutropenia	67 (63%)	54 (50%)	1 (1%)	59 (63%)
Diarrhoea	36 (34%)	49 (46%)	30 (28%)	51 (54%)
Nausea	39 (36%)	41 (38%)	15 (14%)	34 (36%)
Fatigue	29 (27%)	28 (26%)	13 (12%)	24 (26%)
Rash	23 (21%)	28 (26%)	12 (11%)	27 (29%)
Mucosal inflammation	23 (21%)	28 (26%)	3 (3%)	24 (26%)
Myalgia	24 (22%)	24 (22%)	10 (9%)	19 (20%)
Asthenia	19 (18%)	22 (21%)	3 (3%)	15 (16%)
Headache	12 (11%)	12 (11%)	15 (14%)	12 (13%)

Data are n (%).

Table 4: **Summary of the ten most common adverse events (any grade)**

	Trastuzumab plus docetaxel (group A; n=107)	Pertuzumab, trastuzumab, and docetaxel (group B; n=107)	Pertuzumab plus trastuzumab (group C; n=108)	Pertuzumab plus docetaxel (group D; n=94)
Neutropenia	61 (57%)	48 (45%)	1 (1%)	52 (55%)
Febrile neutropenia	8 (7%)	9 (8%)	0	7 (7%)
Leucopenia	13 (12%)	5 (5%)	0	7 (7%)
Diarrhoea	4 (4%)	6 (6%)	0	4 (4%)
Asthenia	0	2 (2%)	0	2 (2%)
Granulocytopenia	1 (1%)	1 (1%)	0	2 (2%)
Rash	2 (2%)	2 (2%)	0	1 (1%)
Menstruation irregular	1 (1%)	1 (1%)	0	4 (4%)
Drug hypersensitivity	0	1 (1%)	2 (2%)	0
ALT increased	3 (3%)	0	0	1 (1%)
Total number of serious adverse events	20	15	4	16
Number of patients with ≥1 serious adverse events	18 (17%)	11 (10%)	4 (4%)	16 (17%)
Neutropenia	1 (1%)	4 (4%)	0	6 (6%)
Febrile neutropenia	7 (7%)	6 (6%)	0	6 (6%)
Neutropenic infection	0	1 (1%)	0	0
Neutropenic sepsis	1 (1%)	0	0	0
Pyrexia	1 (1%)	1 (1%)	0	0
Diarrhoea	2 (2%)	0	0	1 (1%)
Congestive heart failure	0	0	1 (1%)	0
Fulminant hepatitis	0	1 (1%)*	0	0
Other	8 (7%)	2 (2%)	3 (3%)	3 (3%)
Deaths	0	1 (1%)†‡	0	1 (1%)§

Data are n (%). ALT=alanine aminotransferase. *Resulted in patient's death. †Died of fulminant hepatitis. Death occurred in the neoadjuvant setting on day 70. ‡Docetaxel is associated with a rare incidence of fatal hepatitis. §Died of lung metastases and progressive disease in the neoadjuvant setting on day 116.

Table 5: **Most common adverse events of grade 3 or higher and serious adverse events**

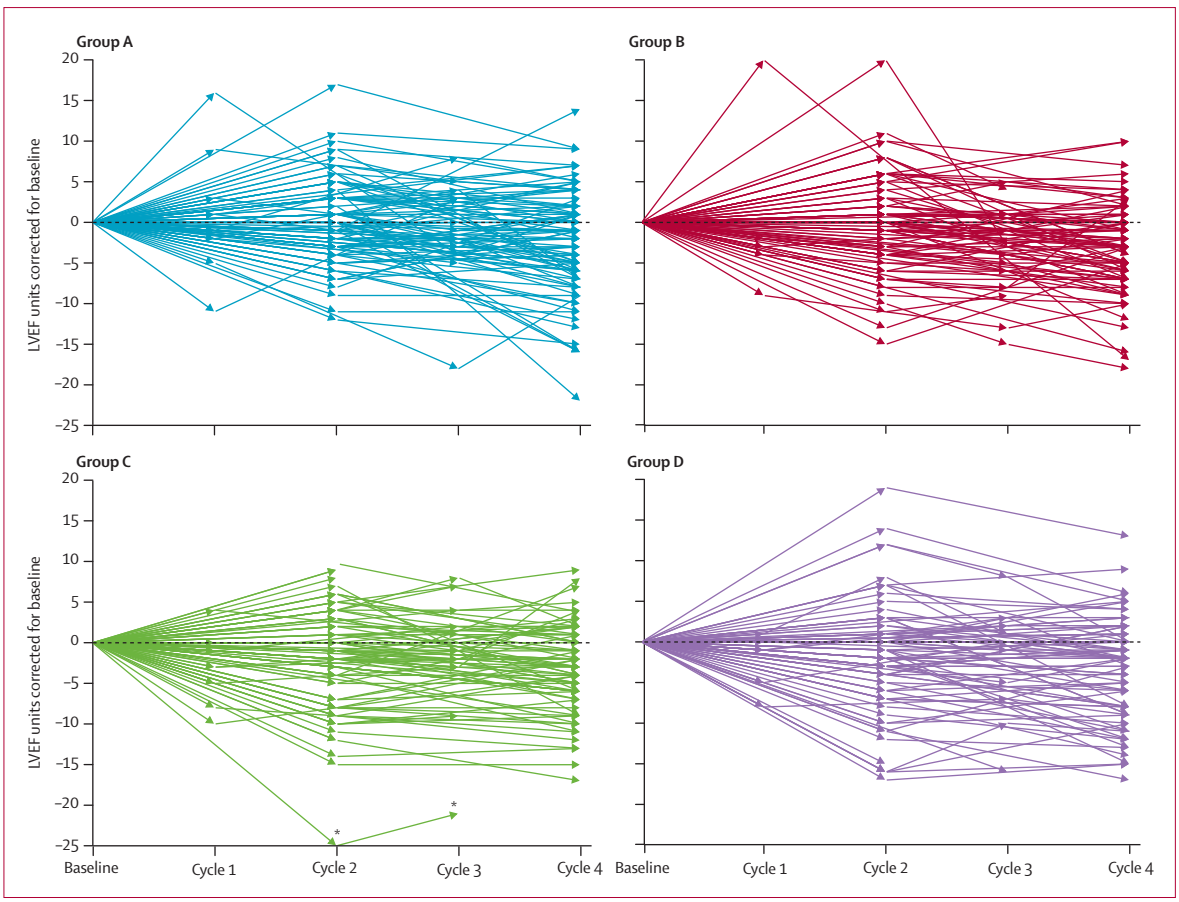

Figure 2: **LVEF changes during neoadjuvant treatment**
LVEF=left ventricular ejection fraction. Group A=trastuzumab plus docetaxel. Group B=pertuzumab and trastuzumab plus docetaxel. Group C=pertuzumab and trastuzumab. Group D=pertuzumab plus docetaxel. LVEF assessments by echocardiography or multiple gated acquisition were planned at baseline and cycles 2 and 4; some patients had additional assessments. The relative LVEF change from baseline is shown for each patient in the four treatment groups. *Patient who developed congestive heart failure and discontinued treatment.

Of these six patients, all had LVEF improvements to more than 50% and a decrease of less than 10% by cycle 4, with the exception of the one patient in group C who discontinued treatment because of congestive heart failure. This patient had a history of hypertension and angina pectoris, had a coronary arterial stent in situ, and was receiving digoxin at baseline. The patient's enrolment into study was a protocol violation.

Discussion

In this study, a significantly higher proportion of women given neoadjuvant pertuzumab and trastuzumab plus docetaxel achieved a pathological complete response in the breast than did those given trastuzumab and docetaxel alone, as measured after only 12 weeks of neoadjuvant treatment in a population in which a third of patients were affected by locally advanced disease.

Although pertuzumab plus docetaxel was efficacious, the combination of chemotherapy with both antibodies was more active than chemotherapy with either antibody alone. The benefit of dual HER2 targeting has also been noted in the NeoALTTO study,[18] in which six cycles of neoadjuvant trastuzumab and the tyrosine-kinase inhibitor lapatinib plus chemotherapy resulted in pathological complete responses in 51·3% of patients, compared with 29·5% of those given trastuzumab plus chemotherapy.[18] Of note, in our study, pathological complete response was achieved in 17% of patients given trastuzumab and pertuzumab without chemotherapy, suggesting that a proportion of HER2-positive tumours can be eradicated without chemotherapy, which might have immediate use for women who cannot receive cytotoxic drugs. However, a third of patients did not respond to the regimen of both antibodies. This could be partly due to the short duration of neoadjuvant treatment. Indeed, results from a study in patients with metastatic breast cancer showed that the conversion of stable disease to objective response was a late event in many patients.[11] The absence of response to the two antibodies in a sizeable proportion of patients highlights the need for predictive biomarkers of response in view of pursuing this chemotherapy-free option.

A potential limitation of the study is that 6% (25 of 417) of patients, mostly in the chemotherapy-free group, did not undergo surgery as planned. Most of these patients did not achieve a sufficient therapeutic response.

Tumour eradication was higher in hormone receptor-negative than in hormone receptor-positive patients. This finding has been reported previously,[14] is similar to observations with chemotherapy treatment,[19] and is usually attributed to the companion chemotherapy. However, in this study, a higher percentage of hormone receptor-negative patients achieved a pathological complete response across all groups, including those patients who did not receive chemotherapy, indicating that the different likelihood of response according to hormone receptor status is an intrinsic characteristic of the tumours. Of note, more patients with hormone receptor-negative tumours achieved pathological complete response with the doublet of pertuzumab and trastuzumab than did those with hormone receptor-positive tumours in all groups. As the duration of neoadjuvant therapy was short, the true benefit in hormone receptor-positive patients might be obscured and should be assessed with longer-term therapy.[14,20,21] A recent meta-analysis[22] of neoadjuvant studies showed that pathological complete response is better correlated with long-term outcome in patients with hormone receptor-negative rather than hormone receptor-positive disease.[22] The phase 2 design and the small sample size of our study will prevent future analyses of outcome in the overall population and in subsets; thus, the study will not contribute to clarification of the actual predictive role of pathological complete response according to hormone receptor status.

Our trastuzumab plus chemotherapy group resulted in a lower rate of pathological complete response than that in other studies that adopted longer regimens and sequential chemotherapy.[14,16] After surgery, all patients in our study received adjuvant conventional treatment including anthracyclines and trastuzumab for 1 year in total to ensure optimum drug therapy.

The tolerability of the triplet regimen of pertuzumab, trastuzumab, and docetaxel was similar to that of conventional trastuzumab plus docetaxel.[23] As expected, bone-marrow toxic effects and febrile neutropenia occurred in all groups that included docetaxel.[23] Cardiac feasibility was good, although a longer observation period will be needed to exclude any further risk from the addition of pertuzumab. The only event of serious cardiac toxic effects (congestive heart failure) was noted in a woman who enrolled despite having coronary stents and receiving digoxin for a pre-existing cardiovascular disease. Cardiac tolerability in the adjuvant phase will be presented separately. Of note, pertuzumab and trastuzumab without docetaxel were associated with only a few adverse events of grade 3 or higher. Because pertuzumab blocks the heterodimer formation responsible for signalling via EGFR and HER2, diarrhoea and skin rash can occur, as noted with other drugs that affect the same pathway, such as the tyrosine-kinase inhibitors, lapatinib and neratinib.[24,25] In the chemotherapy-free group of this study, diarrhoea and skin rash occurred in less than 30% of patients and were of grade 2 or less. The tolerability profile of the chemotherapy-free regimen is similar to that reported in women with metastatic breast cancer,[11] in whom the higher incidence of grade 1–2 diarrhoea and rash (>60%) than in NeoSphere could be due to the extensive previous treatment and the longer duration of study therapy (median of nine cycles of pertuzumab plus trastuzumab).[11]

The success of trastuzumab has prompted the search for more HER2-directed therapies (panel).[24,27–30] The growing list of drugs, the increasing number of promising permutations of new and established treatments, and the rising size and costs of adjuvant trials challenge the conventional approach to investigating every new candidate treatment. The neoadjuvant setting is ideally suited for rapidly testing new HER2-targeted therapies while providing data on pathological response that could act as a surrogate for long-term efficacy.[14,15] Data obtained from NeoSphere supported the conduct and informed the design of an ongoing adjuvant trial with pertuzumab (NCT01358877), and illustrated the potential of the neoadjuvant approach in new drug development.

***Panel:* Research in context**

Systematic review

We searched PubMed with the terms "trastuzumab", "HER2" and "breast cancer" for articles published between 1998, and 2011. Results were manually sorted and restricted to landmark findings regarding relevance to the treatment of HER2-positive early breast cancer. HER2-targeted therapy with trastuzumab is established as the standard of care for HER2-positive early breast cancer, based on four randomised phase 3 trials.[3,4,26] The notion of targeting the HER2 receptor with two drugs with different mechanisms of action is based on solid preclinical data and requires assessment in clinical trials. Neoadjuvant clinical studies allow rapid assessment of the benefit of new treatment regimens, with pathological complete responses acting as a surrogate marker for long-term outcomes.[12,14,15] The NeoSphere study was done to assess whether a blockade of the HER2 signalling pathway with pertuzumab and trastuzumab could improve treatment outcomes in this clinical setting and gain insights for future studies.

Interpretation

In the NeoSphere study, following only four cycles of neoadjuvant treatment, pertuzumab and trastuzumab plus docetaxel resulted in complete tumour eradication in the breast in significantly more women than for those treated with trastuzumab plus docetaxel alone. Importantly, the combination of pertuzumab with trastuzumab and docetaxel did not result in any additional safety signals. Thus, this triplet combination could be an attractive proposition for patients with HER2-positive breast cancer. Additional studies in the neoadjuvant setting—eg, NeoALTTO[18]—have also confirmed the potential of dual HER2-targeted therapy. Taken together, these results suggest that different mechanisms of action of HER2-targeting drugs could provide a more comprehensive blockade of the signalling pathway when combined. NeoSphere also examined a chemotherapy-free regimen of pertuzumab and trastuzumab that resulted in pathological complete responses in a proportion of women and a favourable safety profile. These findings suggest a potential future role for chemotherapy-free HER2-targeted therapy, although such regimens require further clinical investigation and the assessment of predictive biomarkers.

Contributors
LG was involved in study design; protocol development; recruitment and management of patients; data collection, analysis, and interpretation; and writing of the report. PV was involved in study design, protocol development, data analysis and interpretation, and writing of the report. GR was involved in study design, protocol development, data analysis and interpretation, and writing of the report. TS and JR were involved in protocol development, data analysis and interpretation, and writing of the report. TP, Y-HI, LR, L-MT, M-CL, AL, ES, JdlH-R, S-AI, JLP, BP, PM, VSe, VSr, and GB were involved in the discussion of the protocol, recruitment and management of patients, and data collection and analysis. All authors reviewed and approved the manuscript for submission.

Conflicts of interest
LG is an advisory board member for Roche, Genentech, GlaxoSmithKline, Boehringer Ingelheim, Wyeth, and Novartis. GR, TS, and JR are Roche employees. GR and TS have Roche stock ownership interests to disclose. TP and VSr received research support funding from Roche. S-AI participated in a Roche speakers' bureau. Y-HI, LR, L-MT, M-CL, AL, ES, JdlH-R, JLP, BP, PM, VSe, GB, and PV declare that they have no conflicts of interest.

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