Multicentre international open label phase 2 randomised trial, small numbers, 5 yr followup of NeoSphere.
Primary endpoint was reported in previous paper and it does show statistical increase in pathological complete response when pertuzamab is added to trastuzamab and docetaxel. (45.8% B vs 29% A)
Although not powered for secondary endpoints, this paper is reporting the 5 year PF/ DF survival and safety.
5 year PF survival was better (86%) in B than A (81%)
DF survival is consistent with this (84% vs 81%)
Most common severe adverse event was neutropenia across all groups.
Prior to Neosphere, pertuzamab was licenced for use with metastatic breast ca, since this study, pertuzamab is now licensed in patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence

5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial

Group A -T+D
Group B -P+T+D
Group C -P+T
Group D -P+D

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Summary

Background In the primary analysis of the NeoSphere trial, patients given neoadjuvant pertuzumab, trastuzumab, and docetaxel showed a significantly improved pathological complete response compared with those given trastuzumab and docetaxel after surgery. Here, we report 5-year progression-free survival, disease-free survival, and safety.

Methods In this multicentre, open-label, phase 2 randomised trial in hospitals and medical clinics, treatment-naive adults with locally advanced, inflammatory, or early-stage HER2-positive breast cancer were randomly assigned (1:1:1:1) 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 every 3 weeks, increasing to 100 mg/m² from cycle 2 if tolerated; group A), pertuzumab (840 mg loading dose, followed by 420 mg every 3 weeks) and trastuzumab plus docetaxel (group B), pertuzumab and trastuzumab (group C), or pertuzumab and docetaxel (group D). After surgery, patients received three cycles of FEC (fluorouracil 600 mg/m², epirubicin 90 mg/m², and cyclophosphamide 600 mg/m²) every 3 weeks (patients in group C received four cycles of docetaxel prior to FEC), and trastuzumab 6 mg/kg every 3 weeks to complete 1 year's treatment (17 cycles in total). Randomisation was done by a central centre using dynamic allocation, stratified by operable, locally advanced, and inflammatory breast cancer, and by oestrogen and/or progesterone receptor positivity. Safety analyses were done according to treatment received. The primary endpoint (pathological complete response) was previously reported; secondary endpoints reported here are 5-year progression-free survival (analysed in the intention-to-treat population) and disease-free survival (analysed in patients who had surgery). Secondary and exploratory analyses were not powered for formal statistical hypothesis testing, and therefore results are for descriptive purposes only. The study ended on Sept 22, 2014 (last patient, last visit). This study is registered with ClinicalTrials.gov, number NCT00545688.

Findings Between Dec 17, 2007, and Dec 22, 2009, 417 eligible patients were randomly assigned to group A (107 patients), group B (107 patients), group C (107 patients), or group D (96 patients). One patient in group A withdrew before treatment. One patient assigned to group D received group A treatment, one patient assigned to group D received group B treatment, and one patient assigned to group B received group C treatment. At clinical cutoff, 87 patients had progressed or died. 5-year progression-free survival rates were 81% (95% CI 71–87) for group A, 86% (77–91) for group B, 73% (64–81) for group C, and 73% (63–81) for group D (hazard ratios 0·69 [95% CI 0·34–1·40] group B *vs* group A, 1·25 [0·68–2·30] group C *vs* group A, and 2·05 [1·07–3·93] group D *vs* group B). Disease-free survival results were consistent with progression-free survival results and were 81% (95% CI 72–88) for group A, 84% (72–91) for group B, 80% (70–86) for group C, and 75% (64–83) for group D. Patients who achieved total pathological complete response (all groups combined) had longer progression-free survival compared with patients who did not (85% [76–91] in patients who achieved total pathological response *vs* 76% [71–81] in patients who did not achieve total pathological response; hazard ratio 0·54 [95% CI 0·29–1·00]). There were no new or long-term safety concerns and tolerability was similar across groups (neoadjuvant and adjuvant treatment periods combined). The most common grade 3 or worse adverse events were neutropenia (group A: 71 [66%] of 107 patients; group B: 59 [55%] of 107; group C: 40 [37%] of 108; group D: 60 [64%] of 94), febrile neutropenia (group A: 10 [9%]; group B: 12 [11%]; group C: 5 [5%]; group D: 15 [16%]), and leucopenia (group A: 13 [12%]; group B: 6 [6%]; group C: 4 [4%]; group D: 8 [9%]). The number of patients with one or more serious adverse event was similar across groups (19–22 serious adverse events per group in 18–22% of patients).

Interpretation Progression-free survival and disease-free survival at 5-year follow-up show large and overlapping CIs, but support the primary endpoint (pathological complete response) and suggest that neoadjuvant pertuzumab is beneficial when combined with trastuzumab and docetaxel. Additionally, they suggest that total pathological complete response could be an early indicator of long-term outcome in early-stage HER2-positive breast cancer.

Funding F Hoffmann-La Roche.

Lancet Oncol 2016; 17: 791–800

Published Online
May 11, 2016
http://dx.doi.org/10.1016/S1470-2045(16)00163-7

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Research in context

Evidence before this study

The addition of pertuzumab to trastuzumab and docetaxel for the first-line treatment of patients with HER2-positive metastatic breast cancer significantly improved both progression-free survival and overall survival, and led to the approval of pertuzumab, in combination with trastuzumab and docetaxel, in this setting. The primary results of the NeoSphere study showed that pathological complete response in the breast was significantly improved by the addition of pertuzumab to trastuzumab and docetaxel. NeoSphere's results, in combination with the results from the neoadjuvant TRYPHAENA study, led the US Food and Drug Administration in 2013, and more recently the European Medicines Agency in 2015, to grant pertuzumab accelerated approval in the neoadjuvant setting, making pertuzumab the first drug to be approved using pathological complete response as an endpoint. We now report 5-year progression-free survival and disease-free survival results, exploratory associations between total pathological complete response and progression-free survival, and long-term safety. To put the findings of NeoSphere into context with respect to associations between total pathological complete response and clinical benefit, we searched PubMed plus abstracts from the American Society of Clinical Oncology annual meetings, the San Antonio Breast Cancer Symposium annual meetings, the European Society for Medical Oncology biennial meetings, and the European Cancer Congress biennial meetings with the terms "breast cancer", "HER2", "long term", and "pathologic(al) complete response", selecting relevant English-language publications from Dec 1, 2010, to Dec 1, 2015. Studies have shown that pathological complete response in the breast or total pathological complete response is likely to predict clinical benefit in patients with early-stage HER2-positive breast cancer.

Added value of this study

NeoSphere is the first neoadjuvant study of pertuzumab to report mature progression-free survival and disease-free survival data. Furthermore, it adds to the body of evidence suggesting an association between pathological complete response in the breast or total pathological complete response and improved long-term outcomes in early-stage HER2-positive breast cancer.

Implications of all the available evidence

The results from NeoSphere suggest that progression-free survival is improved when neoadjuvant pertuzumab is administered in combination with trastuzumab and docetaxel. It is also noteworthy that disease-free survival after four cycles of neoadjuvant pertuzumab, trastuzumab, and docetaxel seemed to be better than disease-free survival after neoadjuvant docetaxel and trastuzumab despite identical adjuvant therapy. However, these results must be intrepeted with caution as NeoSphere is a phase 2 study, and was not designed or powered to detect differences in survival outcomes. Further trials such as the phase 3 APHINITY trial (NCT01358877), which is assessing pertuzumab, trastuzumab, and chemotherapy in the adjuvant setting, may provide more information on the efficacy of this drug combination in early-stage breast cancer.

Introduction

The clinical benefit of combining the HER2-directed monoclonal antibodies pertuzumab and trastuzumab was first shown in patients with HER2-positive metastatic breast cancer whose disease had progressed during previous trastuzumab therapy.[1] On the basis of those results, pertuzumab, trastuzumab, and chemotherapy were tested in the HER2-positive neoadjuvant setting in the phase 2 NeoSphere[2] and TRYPHAENA studies,[3] and in the phase 3 CLEOPATRA trial in metastatic breast cancer.[4,5] In TRYPHAENA,[3] a high proportion of patients achieved a pathological complete response (57·3–66·2%) with pertuzumab and trastuzumab in combination with standard anthracycline-based and non-anthracycline-based neoadjuvant regimens.In CLEOPATRA,[4,5] first-line treatment with pertuzumab and trastuzumab plus docetaxel significantly improved progression-free survival and overall survival in patients with HER2-positive metastatic breast cancer, compared with placebo, trastuzumab, and docetaxel.

The primary analysis of NeoSphere[2] showed that patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer, who received four cycles of neoadjuvant pertuzumab and trastuzumab plus docetaxel, had a significant improvement (16·8%) in pathological complete response in the breast (defined as absence of invasive cancer in the breast, regardless of ductal carcinoma in situ; 49 [46%] of 107 patients, 95% CI 36·1–55·7), compared with patients who received trastuzumab plus docetaxel (31 [29%] of 107 patients, 20·6–38·5; p=0·0141).[2] Similarly, there was a 17·8% increase in total pathological complete response (defined as absence of invasive cancer in the breast and axillary nodes, regardless of ductal carcinoma in situ) in patients who received pertuzumab and trastuzumab plus docetaxel (42 [39%] of 107 patients, 95% CI 30·0–49·2) compared with patients who received trastuzumab and docetaxel (23 [22%] of 107 patients, 14·1–30·5).[2] NeoSphere also assessed neoadjuvant pertuzumab and trastuzumab without chemotherapy, and pertuzumab plus docetaxel. Both combinations were active but were less so than trastuzumab plus docetaxel or than both antibodies plus docetaxel.[2]

After surgery, patients in NeoSphere received additional chemotherapy and adjuvant trastuzumab to provide all patients with optimal therapy for operable HER2-positive breast cancer.

In this second Article, we report prespecified secondary endpoints of progression-free survival, disease-free survival, and safety in NeoSphere, 5 years after randomisation of the last patient. We also examined the association between total pathological complete response and progression-free survival. Previous studies indicated that pathological complete response is likely to predict clinical benefit in patients with early-stage HER2-positive breast cancer.[6–12] We used total pathological complete response rather than pathological complete response in the breast to align with the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) guidance.[13,14]

Methods

Study design and participants

The study design and patient eligibility criteria have been reported previously.[2] NeoSphere was a randomised, multicentre, international, open-label, phase 2 study. Patients were recruited from 59 centres in 16 countries. Eligible patients had operable (T2–3, N0–1, M0), locally advanced (T2–3, N2–N3, M0; T4a–c, any N, M0), or inflammatory (T4d, any N, M0) HER2-positive breast cancer. Primary tumours were larger than 2 cm in diameter, as measured by mammogram and clinical breast examination, and HER2 positivity was centrally confirmed (immunohistochemistry 3+, or 2+ and positive for fluorescence or chromogenic in-situ hybridisation).

Eligible patients were aged 18 years or older, had a baseline left ventricular ejection fraction of 55% or more, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had not received any previous anti-cancer therapy. Key exclusion criteria were metastatic disease (stage IV) or bilateral breast cancer, other malignancies, impaired liver function, inadequate bone marrow or renal function, impaired cardiac function, uncontrolled hypertension, pregnancy, and refusal to use contraception. There was no protocol-specified exclusion based on life expectancy.

NeoSphere was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Approval for the protocol and any modifications was obtained from independent ethics committees. All patients provided written informed consent. The study protocol is available online.

Randomisation and masking

Randomisation methods have been reported previously.[2] Patients were randomly assigned (1:1:1:1) to one of four neoadjuvant treatment groups, in which patients received trastuzumab plus docetaxel (group A), pertuzumab and trastuzumab plus docetaxel (group B), pertuzumab and trastuzumab (group C), or pertuzumab plus docetaxel (group D).

Group D was added after 29 patients had been recruited to the study to assess the activity of pertuzumab and docetaxel without trastuzumab. Eligible patients were randomly assigned via a central centre (Almac Clinical Technologies, Yardley, PA, USA), using an interactive voice response system and dynamic allocation, stratified by operable, locally advanced, and inflammatory breast cancer, and by oestrogen or progesterone receptor positivity. The trial was open label.

Procedures

All treatment groups received four cycles of neoadjuvant treatment. Neoadjuvant treatment was given intravenously every 3 weeks and consisted of trastuzumab plus docetaxel (group A), pertuzumab and trastuzumab plus docetaxel (group B), pertuzumab and trastuzumab (group C), or pertuzumab plus docetaxel (group D). Trastuzumab was given at 8 mg/kg loading dose followed by 6 mg/kg maintenance dose; pertuzumab was given at an 840 mg loading dose followed by 420 mg maintenance dose; and docetaxel was given at 75 mg/m², increasing to 100 mg/m² from cycle 2 onwards if tolerated. Eligible patients (ie, those who hadn't withdrawn; appendix p 20) then had surgery and assessment of pathological complete response, followed by adjuvant treatment: three cycles of intravenous FEC (fluorouracil 600 mg/m², epirubicin 90 mg/m², and cyclophosphamide 600 mg/m²) every 3 weeks in all groups except for group C, in which patients received four cycles of docetaxel before FEC. All patients received concomitant intravenous trastuzumab 6 mg/kg every 3 weeks to complete 1 year's treatment (17 cycles in total). Radiotherapy and hormone therapy, if indicated, were given in accordance with local guidelines. Dose reductions were not permitted for pertuzumab and trastuzumab. Delays to administration of pertuzumab and trastuzumab were permitted to assess or treat adverse events. During neoadjuvant treatment, only two dose delays of up to 2 weeks each were permitted; during adjuvant treatment, trastuzumab delays were permitted as required. Pertuzumab and trastuzumab infusions could be slowed down (prespecified infusion rate decreased) or interrupted (infusion temporarily stopped and subsequently restarted, usually on the same day but anytime within the same treatment cycle was permitted) for infusion-related symptoms (eg, fever or chills) and resumed once symptoms abated. Docetaxel dose could be reduced from 100 mg/m² to 75 mg/m² and then to 60 mg/m² if non-haematological toxicities worse than grade 2 occurred (excluding alopecia), after which discontinuation was required. A docetaxel dose delay of 2 weeks was permitted per cycle (for myelosuppression, hepatic dysfunction, and other dose-limiting toxicities), with one further dose delay of 2 weeks allowed before study discontinuation was required. Docetaxel infusions could be slowed down or interrupted for minor symptoms such as flushing or local cutaneous reactions and resumed once symptoms abated. FEC dose reductions were allowed in accordance with

See Online for appendix

For the **study protocol** see http://www.roche-trials.com/trialDetailsGet.action?studyNumber=WO20697

the relevant summary of product characteristics. Patients could withdraw from the study at any time for any reason. Investigators could also withdraw patients in the event of intercurrent illness, adverse events, disease progression, protocol violation, cure, administrative reasons, or any other reason.

Clinical breast examinations were done every cycle up to 7 days prior to dosing. Patients had a mammogram and ultrasonography (if required by local practice) before surgery (cycle 4) and 28 days after their last study treatment. Physical examinations were done and vital signs and ECOG performance status were measured every cycle and then every 3 months for 1 year, and every 6 months for 3 years during follow-up. Left ventricular ejection fraction was measured by echocardiography (or multi-gated acquisition) every two cycles during neoadjuvant treatment and every two to three cycles during adjuvant treatment, and then every 6 months for 2 years. Blood counts and laboratory parameters were assessed every cycle and then as needed during follow-up (see study protocol for details). Chest radiography, liver or skeletal ultrasonography, and bone scans were done as needed during follow-up. Adverse events and serious adverse events were monitored continuously until 28 days after the last treatment and were graded according to standard criteria.[15,16] Related adverse events and serious adverse events, and unrelated severe or life-threatening adverse events were still reportable after this period. Symptomatic left ventricular systolic dysfunction grade 3 or worse, reportable as congestive heart failure, was reportable up to 2 years after treatment. Pathological complete response in the breast was assessed locally, and to ensure consistency, blinded data were reviewed by a consultant pathologist at regular intervals.[2] Primary tumour samples were collected at study entry and at surgery to assess biomarkers that could predict response to treatment.

Outcomes

The primary endpoint (pathological complete response in the breast) and the secondary endpoints of clinical response rate, time to clinical response, breast-conserving surgery rate, and safety in the neoadjuvant period were reported in 2012.[2] Biomarker analyses will be reported separately. In this Article, we report the secondary endpoints of progression-free survival (defined as the time from the date of randomisation to the first documentation of progressive disease or death; equivalent to event-free survival),[13] disease-free survival (time from the first date of no disease [ie, date of surgery] to the first documentation of progressive disease or death), and safety for the overall and adjuvant treatment periods. We did exploratory subgroup analyses for progression-free survival by total pathological complete response and hormone receptor status.

Statistical analysis

Patients who were enrolled but did not receive any study treatment were not included in any analyses. We calculated pathological complete response for each group by dividing the number of patients achieving pathological complete response by the intention-to-treat population (all randomly assigned patients). A pathological complete response of 25% was expected in group A and group D and 40% in group B or group C.[17] A sample size of 400 patients was planned to provide 80% power to detect an absolute difference in pathological complete response of 15% between groups. Three comparisons were planned for pathological complete response (group A *vs* group B, group A *vs* group C, and group B *vs* group D) using a two-sided Cochran-Mantel-Haenszel test at an α level of 0·2, stratified by operable, locally advanced, and inflammatory breast cancer and hormone receptor positivity. Formal comparison of group D with group A was not prespecified because group D was added to the study after a protocol amendment.[2]

NeoSphere was not designed or powered to detect treatment differences with respect to secondary efficacy endpoints; therefore, results cannot claim statistical significance and are for descriptive purposes only. We did progression-free survival analyses in the intention-to-treat population and disease-free survival analyses on all patients who underwent surgery. We estimated 5-year progression-free survival and disease-free survival rates for each group using the Kaplan-Meier method. Patients who withdrew without documented progression were censored at the date of the last assessment when they were known to be free from progressive disease or free from disease. We used the Cox proportional hazard model, stratified by operable, locally advanced, inflammatory breast cancer, and hormone receptor-positive disease, to estimate hazard ratios (HRs), and corresponding 95% CIs. We analysed exploratory total pathological complete response–progression-free survival associations using multivariate Cox modelling. We used Statistical Analysis Software version 9.2 for analyses. The safety population included all patients who received at least one dose of study treatment and who had at least one safety assessment done at baseline. For safety analyses patients were assigned to treatment groups as treated. This study is registered with ClinicalTrials.gov, number NCT00545688.

Role of the funding source

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, data analysis, and interpretation. LG, PV, DM, GR, VM, and HD had access to the raw patient data. The corresponding author (LG) was directly involved in the design of the trial, had full access to all of the data, and had the final responsibility to submit for publication. The sponsor funded third-party writing assistance provided by Debbie Briggs.

Results

Between Dec 17, 2007, and Dec 22, 2009, 417 patients were randomly assigned to treatment groups: 107 to group A, 107 to group B, 107 to group C, and 96 to group D.[2] Baseline characteristics were balanced across groups (appendix p 9). Patient disposition (trial profile) is shown in the appendix (p 20). One patient randomly assigned to group D received group A treatment, one patient assigned to group D received group B treatment, and one patient assigned to group B received group C treatment in error. 392 (94%) of 417 patients had surgery as planned, and all those who did so had a valid assessment of pathological response. Time on study was balanced across groups, with most patients on study for 48 months or longer (84 [79%] in group A, 88 [82%] in group B, 86 [80%] in group C, and 69 [72% in group D). At the final clinical cutoff (Oct 20, 2014), median time on study, including post-treatment follow-up, was approximately 60 months (group A: 60·5 months [IQR 53–62]; group B: 61·2 months [59–63], group C: 60·5 months [52–62]; group D: 62·3 [46–64]).

Detailed treatment exposure by group is provided in the appendix (p 10). The median number of neoadjuvant pertuzumab cycles received in groups B, C, and D was 4 (range 1–4, IQR 4–4). 290 (94%) of 309 patients completed the planned four cycles, with 101 (8%) of 1203 cycles delayed, slowed down, interrupted, or discontinued. Most patients completed the planned 17 trastuzumab cycles (98 [92%] of 107 in group A, 89 [83%] of 107 in group B, 88 [81%] of 108 in group C, and 73 [78%] of 94 in group D). The median number of trastuzumab cycles received was 17 (range 1–18, IQR 17–17). One patient in group B received an additional trastuzumab cycle because of a site administration error (recorded as a major protocol violation). The percentage of delayed, slowed down, interrupted, or discontinued trastuzumab cycles was similar across groups (4·7–5·4%). Most delays or interruptions were for one cycle, and nearly all delays lasted 14 days or fewer. The median docetaxel intensity in group C during adjuvant treatment was 29·6 mg/m² per week (range 19–33), close to the planned 31·25 mg/m² per week, and similar to that received during neoadjuvant treatment for groups A, B, and D. 81 (75%) of 108 patients in group C completed four cycles of docetaxel, compared with more than 94% in groups A, B, and D (appendix p 10). The percentage of delayed, slowed down, interrupted, or discontinued docetaxel cycles was similar across groups (13·7–19·6%). Adjuvant FEC was completed in 103 (100%) of 103 patients in group A, 96 (94%) of 102 in group B, 85 (90%) of 94 in group C, and 85 (97%) of 88 in group D. The median number of cycles of FEC received was 3 (range 1–3, IQR 3–3). Radiotherapy to the breast or axilla and adjuvant hormonal treatment were evenly distributed across groups.

At clinical cutoff (5 years), 87 (21%) of 417 patients had progressed or died: 19 (18%) of 107 in group A, 17 (16%) of 107 in group B, 27 (25%) of 107 in group C, and 24 (25%) of 96 in group D. 5-year progression-free survival rates were higher in group B (86% [95% CI 77–91]) than in group A (81% [71–87]; HR 0·69 [95% CI 0·34–1·40]), lower in group C (73% [64–81]) than in group A (HR 1·25 [0·68–2·30]), and lower in group D (73% [63–81]) than in group B (HR 2·05 [1·07–3·93]; figure 1A). Disease-free survival analyses were done on the 392 patients who underwent surgery. Disease-free

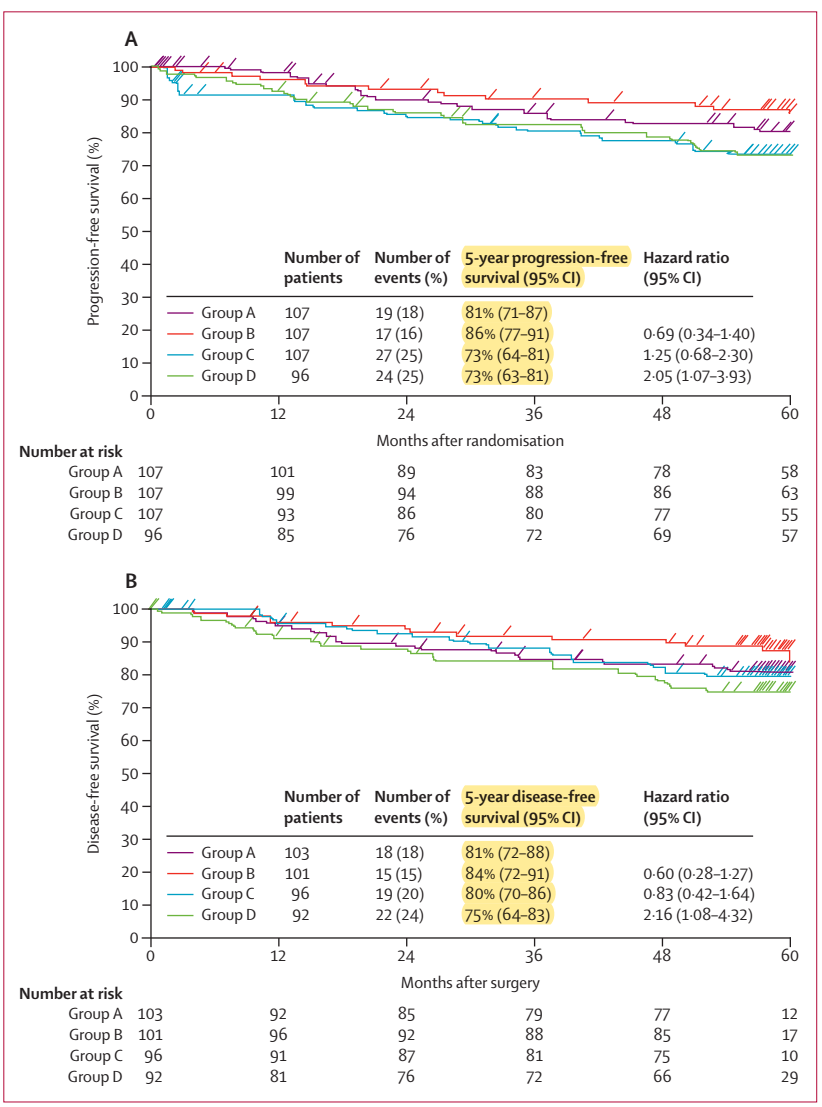

***Figure 1*: Progression-free survival and disease-free survival**

(A) Kaplan-Meier estimates of progression-free survival in the intention-to-treat population, 5 years after random assignment of the final patient. Three late events occurred in group B: two cases of progressive disease at 63 and 71 months, and one death due to an unrelated cerebrovascular accident without progressive disease at 76 months. (B) Kaplan-Meier estimates of disease-free survival in all patients who underwent surgery, 5 years after random assignment of the final patient. The hazard ratio for groups B and C is with respect to group A, whereas the hazard ratio for group D is with respect to group B. Two late events occurred in group B: one case of progressive disease at 67 months, and one death due to an unrelated cerebrovascular accident without progressive disease at 72 months. Tick marks indicate the times at which events were recorded. The Kaplan-Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up. Patients in group A received trastuzumab and docetaxel; group B, pertuzumab, trastuzumab, and docetaxel; group C, pertuzumab and trastuzumab; and group D, pertuzumab and docetaxel.

survival results were consistent with progression-free survival results (figure 1B).

Exploratory subgroup analyses suggested an association between total pathological complete response and progression-free survival when all treatment groups were combined (figure 2A). 94 (23%) of 417 patients achieved total pathological complete response. Of these, 14 (15%) had a progression-free survival event, compared with 73 (23%) of 323 patients who did not achieve total pathological complete response (figure 2A). 5-year progression-free survival rates were 85% (95% CI 76–91) for patients who achieved total pathological complete response, compared with 76% (95% CI 71–81) in patients who did not achieve total pathological complete response (HR 0·54, 95% CI 0·29–1·00; figure 2A).

Results were consistent in each group (figure 2B) and for hormone receptor-negative and hormone receptor-positive disease (figure 2C).

Subgroup analyses of progression-free survival for group B compared with group A were consistent with the findings in the overall population, although the small number of events limits their interpretation (appendix p 22).

Most patients (409 [98%] of 416) had at least one adverse event, of which 403 [97%] of 416 were deemed related to study treatment. The most commonly reported adverse events during the overall treatment period (neoadjuvant plus adjuvant periods) are shown in table 1 and are generally consistent with those reported for the neoadjuvant period.[2] The most common adverse events for the adjuvant period alone are provided in the appendix (p 12), as is a detailed description of adverse events for the overall treatment period (appendix pp 14–18). Adverse events grade 3 and worse that occurred during overall treatment showed the expected chemotherapy toxicity profile (table 1). During adjuvant treatment, adverse events at grade 3 and worse were highest in group C, probably as a result of docetaxel followed by FEC administration (appendix p 12). After adjuvant chemotherapy (ie, during single-agent trastuzumab), the incidence of adverse events of grade 3 and worse was reduced to 7·8–10·6% across all groups, with none of these adverse events reported in more than 5% of patients. During post-treatment follow-up, adverse events were reported in few patients (seven [7%] of 107 in group A, 11 [10%] of 107 in group B, eight [7%] of 108 in group C, and seven [7%] of 94 in group D).

The incidence of serious adverse events during overall treatment was balanced across groups (table 1), but was slightly higher in group C during adjuvant treatment

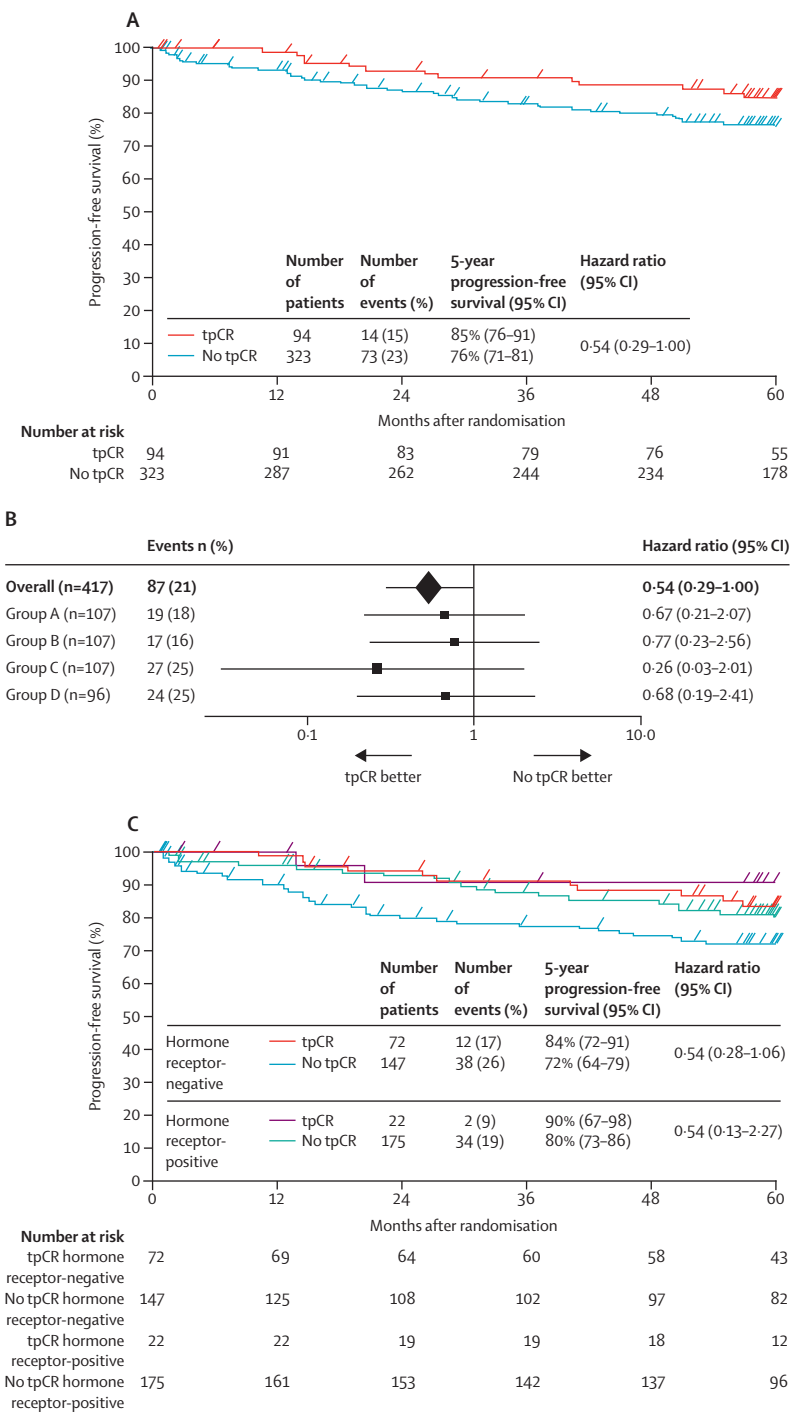

Figure 2: **Exploratory subgroup analyses of progression-free survival according to tpCR**

(A) Kaplan-Meier estimates of progression-free survival according to tpCR for all treatment groups combined. The tick marks indicate the times at which events were recorded. The Kaplan-Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up. One late event occurred in the no total pathological complete response group due to progressive disease at 71 months; one late event occurred in the tpCR group, a death due to an unrelated cerebrovascular accident without progressive disease at 76 months. (B) Hazard ratios and 95% CIs for progression-free survival according to tpCR for each individual group. (C) Kaplan-Meier estimates of progresssion-free survival according to tpCR and hormone receptor status. One late event occurred in the tpCR hormone receptor-negative group, a death due to an unrelated cerebrovascular accident without progressive disease at 76 months; two late events in the no tpCR hormone receptor-positive group due to progressive disease at 63 and 71 months. tpCR=total pathological complete response.

(appendix p 12). Neutropenia and febrile neutropenia were reported most frequently. Two serious adverse events were reported during post-treatment follow-up: myeloproliferative disorder and a cerebrovascular accident resulting in death (considered unrelated to treatment). 31 deaths were reported during the study (appendix p 19). One death occurred during the neoadjuvant period (fulminant hepatitis)[2] and was considered possibly related to study treatment; the remaining 30 occurred during follow-up and were assessed as either unrelated to study treatment or not known. 23 deaths were due to disease progression or breast cancer, two were due to colon or colorectal cancer, one due to cerebrovascular accident, and four had no cause reported.

18 patients discontinued treatment because of study drug-related adverse events: no patients in group A, five (5%) of 107 patients in group B (three from left ventricular dysfunction, one from drug hypersensitivity, and one from abdominal strangulated hernia), eight (7%) of 108 in group C (one from congestive cardiac failure, three from drug hypersensitivity, one from asthenia, one from chest discomfort, one from septic shock, and one due to pregnancy), and five (5%) of 94 in group D (two from left ventricular dysfunction, one from biliary cirrhosis, one from ulcerative colitis, and one from neutropenia).

Few patients (22 [5%] of 416) had cardiac events during the study (table 2). Aside from the previously reported case of congestive heart failure in group C in the neoadjuvant period (that resolved without sequelae following study treatment discontinuation and cardiac drugs),[2] only one other case of left ventricular dysfunction of grade 3 or worse was reported (in group B during the adjuvant period; the patient was asymptomatic). Asymptomatic left ventricular ejection fraction declines of 10% or more from baseline to less than 50% were observed in 20 (5%) of 416 patients (some patients had events in more than one period; table 2). Most events occurred in the adjuvant period, when patients were receiving trastuzumab. All patients with asymptomatic cardiac events recovered to left ventricular ejection fraction of 50% or more without intervention, except for one patient with an asymptomatic left ventricular dysfunction event in group C, who developed this event during follow-up and had not recovered at clinical cutoff.

	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)
Any adverse event	107 (100%)	105 (98%)	103 (95%)	94 (100%)
Alopecia	75 (70%)	73 (68%)	59 (55%)	65 (69%)
Neutropenia	80 (75%)	68 (64%)	47 (44%)	69 (73%)
Nausea	70 (65%)	71 (66%)	52 (48%)	61 (65%)
Diarrhoea	41 (38%)	55 (51%)	46 (43%)	53 (56%)
Fatigue	35 (33%)	35 (33%)	34 (31%)	37 (39%)
Vomiting	31 (29%)	39 (36%)	31 (29%)	37 (39%)
Mucosal inflammation	28 (26%)	33 (31%)	18 (17%)	29 (31%)
Rash	26 (24%)	30 (28%)	22 (20%)	30 (32%)
Myalgia	24 (22%)	25 (23%)	29 (27%)	22 (23%)
Asthenia	22 (21%)	29 (27%)	19 (18%)	23 (25%)
Any grade 3 or worse adverse event	87 (81%)	78 (73%)	65 (60%)	74 (79%)
Neutropenia	71 (66%)	59 (55%)	40 (37%)	60 (64%)
Febrile neutropenia	10 (9%)	12 (11%)	5 (5%)	15 (16%)
Leucopenia	13 (12%)	6 (6%)	4 (4%)	8 (9%)
Menstruation irregular	6 (6%)	4 (4%)	7 (6%)	6 (6%)
Diarrhoea	4 (4%)	7 (7%)	3 (3%)	5 (5%)
Granulocytopenia	1 (1%)	1 (1%)	5 (5%)	2 (2%)
Vomiting	3 (3%)	0	1 (1%)	4 (4%)
Asthenia	1 (1%)	2 (2%)	3 (3%)	3 (3%)
Urinary tract infection	2 (2%)	2 (2%)	1 (1%)	1 (1%)
Radiation skin injury	2 (2%)	2 (2%)	2 (2%)	0
Total number of serious adverse events	25	31	24	26
Number of patients with one or more serious adverse events	21 (20%)	22 (21%)	19 (18%)	21 (22%)
Febrile neutropenia	10 (9%)	8 (7%)	4 (4%)	12 (13%)
Neutropenia	1 (1%)	6 (6%)	3 (3%)	6 (6%)
Pyrexia	1 (1%)	1 (1%)	2 (2%)	1 (1%)
Diarrhoea	2 (2%)	0	0	1 (1%)
Left ventricular dysfunction	0	3 (3%)	0	0
Appendicitis	1 (1%)	0	1 (1%)	0
Neutropenic infection	1 (1%)	1 (1%)	1 (1%)	0
Drug hypersensitivity	0	1 (1%)	1 (1%)	0
Metrorrhagia	1 (1%)	0	1 (1%)	0
Pyelonephritis, acute	0	2 (2%)	0	0
Wound infection	2 (2%)	0	0	0
Other	6 (6%)	9 (8%)	11 (10%)	6 (6%)
Death	0	1 (1%)*	0	0

Data are n (%). The ten most common adverse events, ten most common adverse events of grade 3 or worse, and serious adverse events in two or more patients are reported. *Death in the neoadjuvant period from fulminant hepatitis. Discrepancy with previously published data; one patient in group D withdrew from the study due to disease progression in the neoadjuvant period, not due to death resulting from an adverse event as previously reported.[2]

Table 1: **Most common adverse events, grade 3 or worse adverse events, and serious adverse events during the overall treatment period (neoadjuvant and adjuvant)**

Discussion

In this 5-year follow-up of NeoSphere, the combination of neoadjuvant pertuzumab and trastuzumab plus docetaxel (group B) seemed to improve long-term outcomes for patients compared with trastuzumab plus docetaxel (group A). Although these analyses are not powered for formal statistical hypothesis testing and the results cannot claim statistical significance, the HR estimates for progression-free survival and disease-free survival are supportive of the primary results of pathological complete response in the breast. However, it is important to note that the wide CIs allow for the possibility that group B is not superior to group A. The combination of neoadjuvant pertuzumab and docetaxel (group D) was associated

	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)
Neoadjuvant period	n=107	n=107	n=108	n=94
Left ventricular dysfunction or congestive heart failure (any grade)	1 (1%)	3 (3%)	1 (1%)	1 (1%)
Left ventricular dysfunction or congestive heart failure (grade 3 or worse)	0	0	1 (1%)*	0
LVEF decline to less than 50% and by 10% or more points from baseline	1 (1%)	3 (3%)	1 (1%)	1 (1%)
Adjuvant period	n=103	n=102	n=94	n=88
Left ventricular dysfunction or congestive heart failure (any grade)	1 (1%)	5 (5%)	2 (2%)	5 (6%)
Left ventricular dysfunction or congestive heart failure (grade 3 or worse)	0	1 (1%)†	0	0
LVEF decline to less than 50% and by 10% or more points from baseline	1 (1%)	6 (6%)	0	5 (6%)
Post-treatment follow-up period	n=98	n=102	n=98	n=87
Left ventricular dysfunction or congestive heart failure (any grade)	0	3 (3%)	2 (2%)	2 (2%)
Left ventricular dysfunction or congestive heart failure (grade 3 or worse)	0	0	0	0
LVEF decline to less than 50% and by 10% or more points from baseline	0	3 (3%)	2 (2%)	2 (2%)
Overall treatment and post-treatment follow-up periods combined	n=107	n=107	n=108	n=94
Left ventricular dysfunction or congestive heart failure (any grade)	2 (2%)	9 (8%)	4 (4%)‡	7 (7%)
Left ventricular dysfunction or congestive heart failure (grade 3 or worse)	0	1 (1%)†	1 (1%)*	0
LVEF decline to less than 50% and by 10% or more points from baseline	2 (2%)	9 (8%)	2 (2%)	7 (7%)

Data are n (%). Cardiac event codes to an adverse event of left ventricular dysfunction and congestive heart failure, or LVEF decline. Seven patients experienced LVEF declines in more than one treatment period. All patients who experienced LVEF declines also had an adverse event of left ventricular dysfunction (asymptomatic) or congestive heart failure reported during the study. LVEF=left ventricular ejection fraction. *Neoadjuvant period: congestive heart failure grade 3, New York Heart Association class III. †Adjuvant period: reported as grade 3 but asymptomatic. ‡Post-treatment follow-up period: asymptomatic left ventricular dysfunction event which was ongoing at final analysis.

Table 2: **Cardiac events for neoadjuvant, adjuvant, and post-treatment follow-up periods and for all periods combined**

with slightly worse long-term outcomes for patients (24 progression-free survival events) compared with trastuzumab plus docetaxel (group A, 19 events) and pertuzumab and trastuzumab plus docetaxel (group B, 17 events). It is important to note that the statistical comparison of group D with group A was not prespecified, and is therefore descriptive only.

In NeoSphere, all patients received the same chemotherapy drugs before and after surgery, with the exception of patients in group C, who received all chemotherapy after surgery. All patients received conventional adjuvant trastuzumab to complete 1 year of treatment. Improved disease-free survival after four cycles of neoadjuvant pertuzumab and trastuzumab, plus docetaxel (group B), might suggest a carry-over therapeutic effect that persisted after pertuzumab discontinuation and surgery, and that is unique to the regimen of pertuzumab, trastuzumab, and docetaxel because a similar effect was not observed in the other treatment groups. The enhanced activity of the dual blockade of pertuzumab and trastuzumab might arise from complementary and different mechanisms of action of both antibodies, although the exact mechanism of action is currently unknown.

Exploratory subgroup analyses were consistent with the overall results. Addition of pertuzumab to trastuzumab and docetaxel improved progression-free survival irrespective of total pathological complete response and hormone receptor status. As expected, the magnitude of improvement was greater for patients with hormone receptor-negative disease, in line with the primary outcome results[2] and the CTNeoBC meta-analysis.[7]

FDA guidance[13] states that a large improvement in pathological complete response is likely to predict clinical benefit. Both the FDA and the EMA advise that approval based on pathological complete response might be acceptable in the neoadjuvant setting under specific circumstances.[13,14] In NeoSphere, exploratory subgroup analyses found that, for all groups combined, patients who achieved total pathological complete response had improved progression-free survival. Furthermore, this improvement was seen within each treatment group and occurred irrespective of hormone receptor status. However, these results must be interpreted with caution because there were few events in each group, leading to large variability (wide CIs) around the HR estimates. These results are consistent with the CTNeoBC meta-analysis,[7] and with several studies reporting an association between neoadjuvant HER2 therapy and improved long-term outcomes,[6,8–12] including long-term analysis of the HannaH study[18] (neoadjuvant–adjuvant trastuzumab), in which total pathological complete response was associated with improved event-free survival for both oestrogen receptor-positive and oestrogen receptor-negative or unknown disease.

The results from these previous studies have led to the expectation that positive results in the neoadjuvant setting will be substantiated by large randomised adjuvant studies. However, this was apparently not achieved in the tandem neoadjuvant NeoALTTO[19] and adjuvant ALTTO[20] trials. Results from NeoALTTO[19] showed a significant increase in pathological complete response with neoadjuvant lapatinib plus trastuzumab

versus trastuzumab alone; however, results from ALTTO[20] did not support the benefit: there was no significant improvement in disease-free survival with the same treatment regimen in the adjuvant setting. Of note, the trial designs were different and there were substantial differences in the patient populations. Furthermore, an analysis of the two trials using the FDA's meta-analysis method[7] found no discordance between NeoALTTO and ALTTO and showed that the results of ALTTO are supportive of the relationship between pathological complete response and event-free survival.[21]

An illustration of the power of the neoadjuvant approach in estimating the benefit of new therapies might be derived from the relationship between the odds ratio for pathological complete response of different treatments and the HR for event-free survival, as originally proposed in the CTNeoBC meta-analysis.[7] Results from various trials—including GeparTrio, GeparQuattro, NOAH (Cortazar P, Genentech, personal communication), NeoALTTO,[8,19] and NeoSphere, which reported proportions of patients with pathological complete response and event-free survival—showed that the odds ratio for pathological complete response might be associated with the HR for event-free survival (r^2=0·25; figure 3). This potential association becomes more pronounced when considering only trials that included HER2-targeted therapies (r^2=0·77) and excluding the cluster of empirical chemotherapy trials. Thus, a thorough comparison of pathological complete response in the appropriate setting would be informative and might validate pathological complete response as a surrogate marker of efficacy.

Although achievement of total pathological complete response was associated with improved long-term outcomes, most patients (77%) in NeoSphere did not achieve total pathological complete response. However, residual disease is not necessarily a marker of failure of any neoadjuvant treatment. The 9-year analysis of the National Surgical Adjuvant Breast and Bowel Project[22] Protocol B-18 showed that clinical response (complete or partial response) correlated with long-term outcomes. It is therefore important to note that patients who did not achieve total pathological complete response but received pertuzumab seemed to have longer progression-free survival than those who did not achieve total pathological complete response and did not receive pertuzumab (appendix p 22). The data suggest that pathological complete response is a non-exclusive measure of efficacy of neoadjuvant therapy, and it is not the only measure of benefit of pertuzumab.

There were no new or long-term safety concerns with 5 years of follow-up. The overall tolerability profile was similar across treatment groups and was consistent with that previously reported for the neoadjuvant period[2] and similar to that observed in TRYPHAENA.[3] Importantly, the addition of pertuzumab to trastuzumab and docetaxel during the neoadjuvant period did not seem to result in any additional or long-term cardiotoxicity.

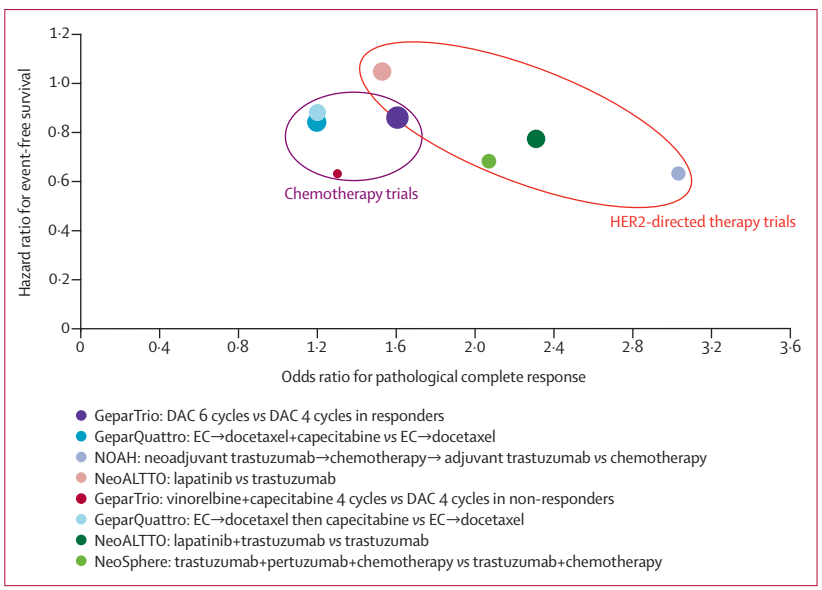

Figure 3: **Association between the effect of chemotherapy and chemotherapy plus HER2-directed therapies on pathological complete response and event-free survival**
Data derived from CTNeoBC (Cortazar P, Genentech, personal communication) and from NeoALTTO.[8,19] The sizes of the circles are proportional to the analysed population sizes. DAC=docetaxel, doxorubicin, and cyclophosphamide. EC=epirubicin and cyclophosphamide.

In summary, the long-term results of NeoSphere are encouraging. Although for descriptive purposes only, they support the primary analysis of pathological complete response in the breast and suggest that four cycles of neoadjuvant pertuzumab is also beneficial in terms of long-term efficacy, when combined with trastuzumab and docetaxel, despite the use of identical adjuvant therapy. The neoadjuvant safety profile was maintained with long-term follow-up. The ongoing phase 3 APHINITY trial (NCT01358877) will assess pertuzumab, in combination with trastuzumab and chemotherapy, in the adjuvant setting. Overall, the results of NeoSphere provide new insight into the association between total pathological complete response and long-term outcomes and support the use of total pathological complete response as a primary endpoint and early indicator of benefit in future neoadjuvant studies of HER2-targeted agents.[13,23]

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. VM was involved in protocol development, review and management of clinical data, data analysis and interpretation, and writing of the report. HD was involved in data collection, figure generation, data analysis and interpretation, and writing of the report. DM was involved in data analysis and interpretation and writing of the report. TP, Y-HI, L-MT, M-CL, AL, ES, JdlH-R, S-AI, JLP, BP, PM, VSe, VSr, and GVB were involved in the discussion of the protocol, recruitment and management of patients, and data collection and interpretation. All authors reviewed and approved the manuscript for submission.

Declaration of interests
LG is an advisory board member for Roche, Genentech, Tahio, Novartis, Synthon, Pfizer, Tiziana Life Sciences, Genomic Health, Medivation, Boehringer Ingelheim, and Celegene. VM is a current employee of Roche, and reports Roche stock ownership interests. HD is a current employee of Roche. GR was a full-time employee of Roche during the design and conduct of NeoSphere. TP reports grants and personal fees from Roche. S-AI reports grants from AstraZeneca. AL reports personal fees from Novartis, Roche, and Pfizer. PV reports grant from Roche. Y-HI, L-MT, M-CL, ES, JdlH-R, JLP, BP, PM, VSe, GVB, VSr, and DM declare no competing interests.

Acknowledgments
This was a collaborative study between Fondazione Michelangelo and F Hoffmann-La Roche. Support for third-party writing assistance for this manuscript, furnished by Debbie Briggs, was provided by F Hoffmann-La Roche. A full list of NeoSphere investigators is provided in the appendix. We thank all patients and investigators who participated in this trial and also the central testing laboratories: Targos Molecular Pathology GmbH, Kassel, Germany, and Roche TRS DNS and protein laboratories, Basel, Switzerland.

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