

# Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study



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## Summary

**Background** A subcutaneous formulation of pertuzumab and trastuzumab with recombinant human hyaluronidase (pertuzumab, trastuzumab, and hyaluronidase-zzxf) was approved by the US Food and Drug Administration (FDA) on June 29, 2020. We report the primary analysis of the FeDeriCa study, which was designed to assess the pharmacokinetics, efficacy, and safety of the fixed-dose subcutaneous formulation compared to intravenous pertuzumab plus trastuzumab in patients with HER2-positive early breast cancer in the neoadjuvant–adjuvant setting.

**Methods** FeDeriCa, a randomised, open-label, international, multicentre, non-inferiority, phase 3 study, was done across 106 sites in 19 countries. Patients aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 or 1, HER2-positive, operable, locally advanced, or inflammatory stage II–IIIC breast cancer, and a left ventricular ejection fraction of 55% or more were randomly assigned (1:1), using a voice-based or web-based response system, to receive intravenous pertuzumab (840 mg loading dose, followed by 420 mg maintenance doses) plus intravenous trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance doses) or the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (1200 mg pertuzumab plus 600 mg trastuzumab loading dose in 15 mL, followed by 600 mg pertuzumab plus 600 mg trastuzumab maintenance doses in 10 mL), both administered every 3 weeks with neoadjuvant chemotherapy. Patients were stratified by hormone receptor status, clinical stage, and chemotherapy regimen. The investigator selected one of the two protocol-approved standard chemotherapy regimens before randomisation. Four cycles of HER2-targeted therapy were administered concurrently with the taxane. After surgery, patients continued the HER2-targeted therapy to receive an additional 14 cycles (total of 18). The primary endpoint was non-inferiority of the cycle 7 pertuzumab serum trough concentration ( $C_{trough}$ ; ie, cycle 8 predose pertuzumab concentration) within the fixed-dose combination for subcutaneous injection versus intravenous pertuzumab plus trastuzumab in the per-protocol pharmacokinetic population (all enrolled patients who adhered to prespecified criteria for pharmacokinetic assessment). Non-inferiority was concluded if the lower bound of the 90% CI of the geometric mean ratio was 0·8 or higher. The safety population included all patients who received at least one dose of study medication, including chemotherapy or HER2-targeted therapy. Enrolment, neoadjuvant therapy, and surgery have been completed; adjuvant treatment and follow-up are ongoing. The trial is registered with ClinicalTrials.gov, NCT03493854.

**Findings** Between June 14, 2018, and Dec 24, 2018, 252 patients were randomly assigned to the intravenous infusion group and 248 to the fixed-dose combination group. The geometric mean ratio of pertuzumab serum  $C_{trough}$  subcutaneous to serum  $C_{trough}$  intravenous was 1·22 (90% CI 1·14–1·31). The most common grade 3–4 adverse events occurring during neoadjuvant treatment with HER2-targeted therapy plus chemotherapy in 5% or more of patients were neutropenia (34 [13%] of 252 patients in the intravenous infusion group vs 35 [14%] of 248 patients in the fixed-dose combination group), decreased neutrophil count (31 [12%] vs 27 [11%]), febrile neutropenia (14 [6%] vs 16 [6%]), diarrhoea (12 [5%] vs 17 [7%]), and decreased white blood cell count (18 [7%] vs nine [4%]). At least one treatment-related serious adverse event was reported in 25 (10%) patients in the intravenous infusion group and 26 (10%) patients in the fixed-dose combination group. One patient in each treatment group had an adverse event that led to death (urosepsis in the intravenous infusion group and acute myocardial infarction in the fixed-dose combination group); neither death was related to HER2-targeted therapy.

**Interpretation** The study met its primary endpoint: the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection provides non-inferior cycle 7 pertuzumab serum  $C_{trough}$  concentrations to intravenous pertuzumab plus trastuzumab in the neoadjuvant setting with comparable total pathological complete response rates, supporting the FDA approval. Safety was similar between treatment groups, and in line with other

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See Online for appendix

**pertuzumab, trastuzumab, and chemotherapy trials. Follow-up is ongoing for long-term outcomes, including efficacy and long-term safety.**

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## Introduction

HER2 overexpression occurs in about 15–20% of breast cancers and is associated with high disease recurrence and short survival.<sup>1,2</sup> Combining intravenous pertuzumab with trastuzumab and chemotherapy for patients with HER2-positive breast cancer led to significantly improved overall survival in CLEOPATRA (metastatic),<sup>3</sup> improved pathological complete response rates in NeoSphere (neoadjuvant),<sup>4</sup> and a clinically meaningful improvement in invasive disease-free survival in patients at high risk of recurrence in APHINITY (adjuvant curative).<sup>5</sup> Hence, pertuzumab plus trastuzumab and chemotherapy is standard treatment for patients with HER2-positive early and metastatic breast cancer.

Intravenous pertuzumab is infused over 30–60 min and trastuzumab over 30–90 min, usually for multiple cycles over a treatment course ( $\leq 1$  year in early breast cancer; until progression in metastatic breast cancer). Establishing intravenous access is invasive, which is inconvenient and painful for patients, especially those who are treated repeatedly.<sup>6,7</sup> Increased use of intravenous monoclonal antibodies in oncology has placed a strain on medical centres' time, as well as on the resources required to prepare and administer infusions and dispose of associated materials.<sup>8</sup>

Available data from studies of monoclonal antibodies administered by subcutaneous injection (subcutaneous trastuzumab and rituximab/hyaluronidase human) have shown that a change in the route from intravenous infusion results in non-inferior serum trough concentration ( $C_{trough}$ ), consistent antitumour activity, and comparable safety.<sup>9–18</sup> Intravenous pertuzumab with subcutaneous trastuzumab injection into the thigh offers a more convenient option (2–5 min administration time), while maintaining similar efficacy and safety to intravenous pertuzumab plus trastuzumab.<sup>19</sup>

Subcutaneous injection reduces the administration burden and time patients spend in infusion chairs, has the potential to optimise medical resource use,<sup>8,20</sup> is preferred by patients, and is more satisfactory for health-care professionals.<sup>12,13,17,21</sup> Subcutaneous injection might also potentially allow home administration: several studies have shown cost, resource, and quality-of-life benefits.<sup>22,23</sup> Efforts are ongoing to assess the feasibility of administering monoclonal antibodies at home.

A fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (pertuzumab, trastuzumab, and hyaluronidase-zzxf) was approved by the US Food and Drug Administration to offer patients less invasive and faster pertuzumab and trastuzumab administration than with individual intravenous infusions.

## Research in context

### Evidence before this study

We searched PubMed with the search terms “pertuzumab”, “trastuzumab”, “HER2-positive”, “early breast cancer”, and “subcutaneous”, restricting results to phase 1–3 prospective clinical trials published in English between Jan 1, 2010, and June 19, 2020. The search confirmed that subcutaneous trastuzumab is a valid alternative treatment to intravenous trastuzumab in HER2-positive breast cancer, with non-inferior serum trough concentrations and pathological complete response rates, and a similar safety profile to intravenous trastuzumab in the neoadjuvant setting. Consistency of efficacy and safety was further supported by results in the adjuvant and metastatic settings, and in combination with chemotherapy with or without pertuzumab. Patients preferred subcutaneous over intravenous trastuzumab. Health-care professionals were also more satisfied with subcutaneous trastuzumab, and additionally referenced savings of time and resources for patients and clinics. Safety when switching from intravenous to subcutaneous trastuzumab, and vice versa, was not impacted. The development of a fixed-dose combination of pertuzumab and trastuzumab for

subcutaneous injection (pertuzumab, trastuzumab, and hyaluronidase-zzxf) was proven feasible; most patients preferred it to intravenous pertuzumab plus trastuzumab; and it was generally well tolerated, even when switching between formulations.

### Added value of this study

The results of this study add to the current knowledge regarding the subcutaneous delivery of monoclonal antibodies in oncology by confirming that the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection provides non-inferior serum trough concentrations to intravenous pertuzumab plus trastuzumab in the neoadjuvant setting, with comparable total pathological complete response rates and a comparable safety profile.

### Implications of all the available evidence

Overall, the evidence shows that subcutaneous administration of monoclonal antibodies offers a faster, more convenient, and less invasive treatment option for HER2-positive breast cancer than do intravenous infusions.

It has identical active ingredients to the intravenous formulations. Because the intravenous pertuzumab regimen is assumed to saturate HER2 receptor binding, predicting maximum clinical efficacy of a subcutaneous dose with a non-inferior steady-state  $C_{trough}$  should be appropriate; a non-inferior  $C_{trough}$  would ensure at least the same degree of target saturation as with intravenous administration, ensuring similar efficacy.<sup>24</sup>

The fixed-dose combination is injected as a non-weight-based dose, similar to intravenous pertuzumab and subcutaneous trastuzumab, but with a shorter administration time (approximately 5–8 min vs 30–90 min for each intravenous infusion). The pertuzumab dose within the fixed-dose combination was established in a phase 1b dose-finding study, which showed that a single 600 mg subcutaneous dose provides similar serum  $C_{trough}$  and area under the concentration–time curve (AUC) values to those of a single 420 mg intravenous dose.<sup>24</sup> The 600 mg trastuzumab dose within the fixed-dose combination was established in a phase 1 study and confirmed in the phase 3 HannaH trial.<sup>9</sup>

We report primary results from FeDeriCa, a pivotal study designed to assess the pharmacokinetics, efficacy, and safety of the subcutaneous injection of the fixed-dose combination compared to intravenous infusion in patients with HER2-positive early breast cancer in the neoadjuvant–adjuvant setting.

## Methods

### Study design and participants

FeDeriCa, a randomised, open-label, international, multi-centre, non-inferiority, phase 3 trial, was done across 106 sites, which were a mixture of academic and community hospitals, in 19 countries (appendix pp 2–6). Eligible patients had HER2-positive early breast cancer and were candidates for preoperative neoadjuvant treatment. Selection criteria were similar to those used in previous intravenous studies: age 18 years or older; operable, locally advanced, or inflammatory HER2-positive (immunohistochemistry 3+ or in-situ hybridisation-positive) stage II–IIIC breast cancer with a primary tumour more than 2 cm in diameter, or node-positive disease; Eastern Cooperative Oncology Group performance status 0 or 1; and a left ventricular ejection fraction (LVEF) of 55% or more (by echocardiography or multiple-gated acquisition scan). HER2 and hormone receptor status were confirmed centrally. Patients were ineligible if they had received any systemic therapy for treatment or prevention of breast cancer, or radiotherapy for cancer. Patients were also ineligible if they had a serious cardiac condition, impaired liver function (serum [total] bilirubin  $>1.25 \times$  upper limit of normal [ULN]; in cases of Gilbert's syndrome, a total bilirubin of  $2 \times$  ULN was permitted; aspartate aminotransferase or alanine aminotransferase [or both]  $>1.25 \times$  ULN; albumin  $<25$  g/L), or inadequate renal (serum creatinine  $>1.5 \times$  ULN) or bone marrow function (absolute neutrophil count  $<1.5 \times 10^9$  cells per L;

platelet count  $<100 \times 10^9$  cells per L; and haemoglobin  $<9$  g/dL).

The study was done in conformance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was reviewed and approved by the institutional review board or ethics committee at each study site. All amendments affecting trial recruitment and conduct were approved. The protocol is available in the appendix (p 23). All patients provided written, informed consent.

### Randomisation and masking

This study was open label. Patients were randomly assigned (1:1) in permuted blocks to receive intravenous infusions or subcutaneous injections via a central voice-based or web-based response system. Stratification factors were hormone receptor status (oestrogen or progesterone receptor-positive, or oestrogen and progesterone receptor-negative); clinical stage (II–IIIA or IIIB–IIIC); and chemotherapy regimen (dose-dense doxorubicin plus cyclophosphamide [ddAC] every 2 weeks followed by paclitaxel every week, or doxorubicin plus cyclophosphamide [AC] every 3 weeks followed by docetaxel every 3 weeks).

### Procedures

Treatment consisted of eight neoadjuvant chemotherapy cycles, comprising four ddAC cycles (doxorubicin 60 mg/m<sup>2</sup> plus cyclophosphamide 600 mg/m<sup>2</sup> every 2 weeks, with granulocyte colony-stimulating factor as needed according to local guidelines) followed by paclitaxel 80 mg/m<sup>2</sup> once weekly for 12 weeks, or four AC cycles (doxorubicin 60 mg/m<sup>2</sup> plus cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks) followed by four docetaxel cycles 75–100 mg/m<sup>2</sup> every 3 weeks (appendix p 7). The choice between chemotherapy regimens was at the investigator's discretion before randomisation. Four intravenous or subcutaneous cycles of HER2-targeted therapy were administered at 3-week intervals concurrently with the taxane component of either regimen. The choice of chemotherapy was due to an anthracycline and a taxane being given for eight cycles with pertuzumab plus trastuzumab, starting on the fifth cycle, whereas docetaxel plus carboplatin would be given for six cycles with pertuzumab plus trastuzumab, starting with the first cycle. Due to the different number of cycles and start of pertuzumab plus trastuzumab, docetaxel and carboplatin was not included because this would have made the pharmacokinetic sampling more complicated and probably would have increased the errors in the timing of the sampling. After completion of the neoadjuvant regimen, patients underwent surgery, followed by a further 14 intravenous or subcutaneous cycles (maximum total of 18) of HER2-targeted therapy. Treatment was to be discontinued in cases of investigator-assessed radiographic or clinical disease progression or recurrence, or unmanageable toxicity. The only mandatory radiography assessments (a bilateral mammogram or other imaging

method [eg, MRI or ultrasound] as per local practice) before the primary analysis were at screening and cycle 8. Any other tumour assessments were carried out according to local practice.

For patients in the intravenous infusion group, pertuzumab was administered as an initial 840 mg loading dose followed by 420 mg maintenance doses every 3 weeks. Intravenous trastuzumab was administered as an initial 8 mg/kg loading dose followed by 6 mg/kg maintenance doses every 3 weeks. The order in which the drugs were administered was according to investigator preference. Chemotherapy was given after HER2-targeted treatment on the same day.

For patients in the fixed-dose combination group, the fixed-dose combination was administered as an initial 1200 mg pertuzumab plus 600 mg trastuzumab loading dose in 15 mL followed by 600 mg pertuzumab plus 600 mg trastuzumab maintenance doses in 10 mL every 3 weeks. The loading dose was selected on the basis of approximate dose proportionality of data in the dose-finding, phase 1 BO30185 study.<sup>24</sup> The fixed-dose combination contained 2000 U/mL recombinant human hyaluronidase (rHuPH20). Subcutaneous injections were administered in the thigh with a hand-held syringe at a rate of about 2 mL/min over 8 min (loading dose) and 5 min (maintenance doses) followed by a 30 min observation period after the first dose and, if well tolerated, 15 min after subsequent doses (appendix p 7).

Dose modifications of HER2-targeted therapy were not permitted. Patients were withdrawn from all study treatment if HER2-targeted therapy was withheld for more than two cycles (>9 weeks between doses) or needed to be permanently discontinued because of treatment-related toxicity.

Patients who discontinued chemotherapy due to toxicity were not automatically withdrawn from study treatment. In such events, surgery could be brought forward and the assigned HER2-targeted therapy was to be completed up to a maximum of 18 cycles, as per the schedule.

Blood samples for pharmacokinetic assessments were collected before intravenous infusion or subcutaneous injection of HER2-targeted therapy, and after administration (appendix p 9). Exact collection times were recorded for pharmacokinetic samples.

Concerning safety, incidence and severity of adverse events, serious adverse events, and laboratory test abnormalities determined according to the US National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4) were assessed continually until treatment completion or the discontinuation visit.

Samples were collected for detection of antidrug antibodies against pertuzumab, trastuzumab, and rHuPH20 (in the fixed-dose combination group) at baseline, during treatment, and during the post-treatment follow-up phase. Antidrug antibodies against pertuzumab and

trastuzumab were detected in serum samples using validated ELISAs. Antibodies against rHuPH20 were detected in plasma samples using a validated electrochemiluminescent assay. All immunogenicity samples were analysed in a central laboratory.

## Outcomes

The primary objective was non-inferiority of the cycle 7 (ie, the concentration measured at predose cycle 8) pertuzumab serum  $C_{trough}$  within the fixed-dose combination versus intravenous pertuzumab. Non-inferiority of cycle 7 trastuzumab serum  $C_{trough}$  within the fixed-dose combination versus intravenous trastuzumab (tested hierarchically with the primary endpoint to adjust for multiple statistical testing) was a secondary endpoint. Cycle 7 (predose cycle 8) was chosen as patients would have received three doses of pertuzumab plus trastuzumab, and would have reached steady-state pertuzumab (and trastuzumab) concentrations. Additionally, this timepoint was matched to the total pathological complete response assessment below, giving both exposure and pharmacokinetic data and matching efficacy data. Key protocol-specified exploratory pharmacokinetic endpoints included maximum serum concentration ( $C_{max}$ ) of pertuzumab and trastuzumab, time to  $C_{max}$  ( $T_{max}$ ), and AUC from 0–21 days ( $AUC_{0-21\text{ days}}$ ).

Concerning efficacy, the main endpoint was total pathological complete response (defined as eradication of invasive disease in the breast and axilla, according to local pathologist assessment [ypT0/is, ypN0]). Additional secondary efficacy endpoints not reported here were invasive disease-free survival (time from the first date of no disease [ie, the date of primary surgery] to the first occurrence of invasive disease or death from any cause), invasive disease-free survival including second primary non-breast cancer (defined in the same way as invasive disease-free survival but including second primary non-breast invasive cancer as an event [with the exception of non-melanoma skin cancers and in-situ carcinoma of any site]), event-free survival (time from enrolment to the first occurrence of breast cancer progression, recurrence, or death from any cause), event-free survival including second primary non-breast cancer, distant recurrence-free interval (time between surgery and the date of distant breast cancer recurrence), and overall survival (time from randomisation to death from any cause). Time-to-event endpoints will be reported at a later date once data are mature.

Clinical responses, defined as complete response, partial response, stable disease, or progressive disease by the investigator as per routine clinical practice by clinical examination or mammography, was a prespecified exploratory efficacy endpoint. Safety was a secondary objective. Primary cardiac safety endpoints were defined as incidence of symptomatic ejection fraction decreases (ie, heart failure) of New York Heart Association (NYHA) class III or IV and a drop in LVEF of 10 percentage points

or more from baseline and to an absolute value of less than 50%, and cardiac death. The incidence of asymptomatic or mildly symptomatic left ventricular systolic dysfunction (NYHA class II heart failure), defined as a decrease in LVEF of 10 percentage points or more to an absolute LVEF of less than 50%, confirmed by a second assessment, was also reported as a secondary cardiac endpoint. The final efficacy and safety analyses are planned to occur 3 years after the last patient has completed treatment. Associations between antidrug antibodies and total pathological complete response and safety were assessed in an exploratory manner, as prespecified in the protocol.

### Statistical analysis

The study was designed to have at least 80% power to demonstrate non-inferiority of the cycle 7 serum  $C_{trough}$  of pertuzumab when administered as part of the fixed-dose combination versus pertuzumab as part of intravenous pertuzumab plus trastuzumab. Assuming a coefficient of variation (CV) of 60% for pertuzumab serum  $C_{trough}$ , based on previous studies, a minimum of 130 patients per study group (total of 260 patients) were needed to demonstrate non-inferiority with 80% power if the true means of the two formulations did not differ by more than 5%. Given that total pathological complete response and safety are both important endpoints in neoadjuvant trials, the sample size was increased to provide a sufficient number of patients to assess and discuss total pathological complete response rates using a precision-based approach and to ensure a robust safety database. Thus, the overall planned enrolment was 500 patients (250 per group), which was considered to be a suitable sample size to provide not only the minimum required for the primary pharmacokinetic non-inferiority analysis, but also to provide a sufficient number of patients for precision-based estimates for the assessment of total pathological complete response and safety.

The primary analysis was done when all patients completed neoadjuvant therapy and underwent surgery (unless prematurely withdrawn). The primary pharmacokinetic analysis was done in the per-protocol pharmacokinetic population, which included all enrolled patients who adhered to prespecified criteria for pharmacokinetic assessment (patients were excluded if they were missing the cycle 7  $C_{trough}$  [ie, predose cycle 8] pharmacokinetic sample, had a  $C_{trough}$  sample collected with  $\geq 2$  days deviation from the planned date on day 21 [ie, before day 19 or after day 23], were given a dose amount that deviated from the planned dose by more than 20% within 3 cycles [from cycle 5], had a dose delay of more than 7 days, were given a subcutaneous injection not in the thigh, had cycle 8 predose and post-dose samples switched in the intravenous infusion group, or if there was an assay error affecting  $C_{trough}$  measurement). Efficacy analyses were done in the intention-to-treat population,

which comprised all patients who underwent randomisation. The safety population included all patients who received at least one dose of study medication, including chemotherapy or HER2-targeted therapy.

The primary objective of this study was to demonstrate non-inferiority—ie, to show that the study drug is not materially worse than the control (one-sided hypothesis). Hence, we assessed the primary pharmacokinetic endpoint, non-inferiority, with a one-sided testing procedure. Non-inferiority was concluded if the lower bound of the two-sided 90% CI of the observed geometric mean ratio (GMR) of the cycle 7 pertuzumab serum  $C_{trough}$  subcutaneous to  $C_{trough}$  intravenous was 0.8 or higher.<sup>25</sup>

The non-inferiority of the subcutaneous and intravenous doses of trastuzumab was assessed using the same criteria as for the primary analysis and was tested in a hierarchical procedure to control the type I error rate at a one-sided significance level of 5%. Thus, we only tested the trastuzumab predose cycle 7 serum  $C_{trough}$  subcutaneous to serum  $C_{trough}$  intravenous ratio if non-inferiority was concluded for the primary endpoint.

We analysed efficacy and safety endpoints descriptively. We calculated total pathological complete responses in each treatment group, between treatment group differences, and corresponding 95% Hauck-Anderson CIs. The lower bound of the 95% CI was used to reflect the largest total pathological complete response difference that could be considered unlikely. We also did a prespecified exploratory subgroup analysis of total pathological complete response.

As part of a post-hoc exploratory analysis, we did a multiple logistic regression analysis of total pathological complete response, adjusting for the stratification factors and selected baseline characteristics (age, race, menopausal status, and bodyweight) to investigate whether the results were still consistent with the unadjusted result.

Statistical analyses were done with SAS software (version 9.4).

This study is registered with ClinicalTrials.gov, NCT03493854.

### Role of the funding source

The funders of the study had a role in the study design, provision of study drugs, protocol development, regulatory and ethics approvals, safety monitoring, data collection, data analysis, data interpretation, and writing of the report, in collaboration with the study authors. All authors had full access to all study data and had final responsibility for the decision to submit for publication.

### Results

Between June 14, 2018, and Dec 24, 2018, 252 patients were randomly assigned to the intravenous infusion group and 248 patients to the fixed-dose combination group. At clinical cutoff on July 4, 2019, enrolment was complete, all patients had completed neoadjuvant

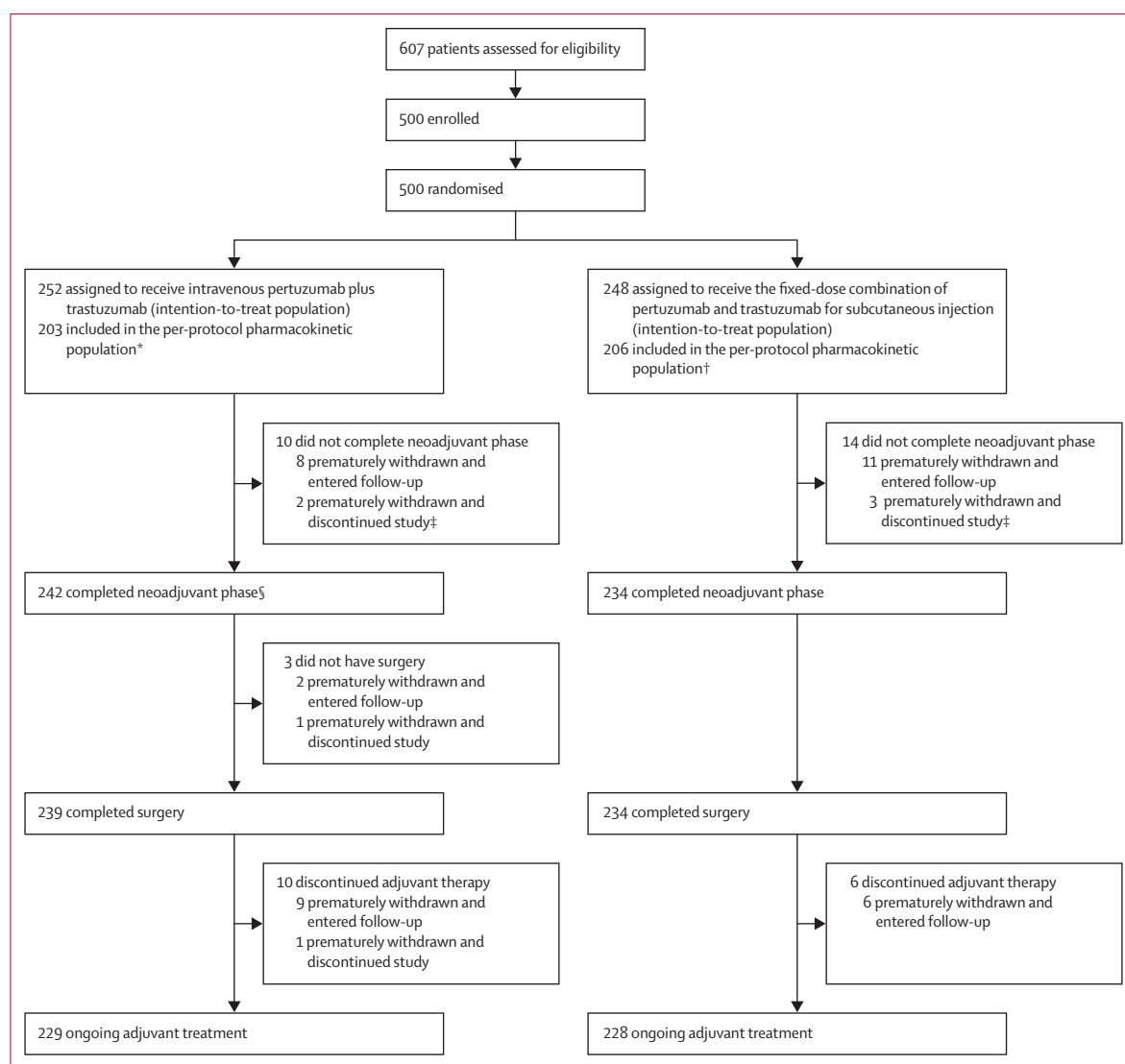


**Figure: Trial profile**

$C_{\text{trough}}$ =serum trough concentration. \*Reasons for exclusion from the per-protocol pharmacokinetic population in the intravenous infusion group were: 13 patients had their  $C_{\text{trough}}$  sample collected with at least 2 days deviation from the planned-on day 21, 17 patients had a dose delay of more than 7 days, cycle 8 predose and post-dose samples were switched in six patients, and two patients had a dose amount that deviated from the planned dose by more than 20% (patients could be counted in more than one category). †Reasons for exclusion from the per-protocol pharmacokinetic population in the fixed-dose combination group were: 17 patients had their  $C_{\text{trough}}$  sample collected with at least 2 days deviation from the planned-on day 21, nine patients had a dose delay of more than 7 days, one patient had a dose amount that deviated from the planned dose by more than 20%, and a subcutaneous injection site other than the thigh was used in two patients (patients could be counted in more than one category). ‡Includes one patient who died. §Three patients discontinued the study before undergoing surgery. One patient missed cycle 7 (ie, did not receive four cycles of HER2-targeted therapy); hence, the patient was excluded from exposure results but continued on to surgery and the rest of the study.

treatment, had undergone surgery, and had started adjuvant therapy, but none had completed follow-up (figure).

Baseline demographic and tumour characteristics were generally well balanced in the intention-to-treat population (table 1) and in the per-protocol pharmacokinetic population (appendix p 10). Overall, baseline characteristics were also balanced between the patients who received the two types of chemotherapy; however, more Asian patients received AC followed by docetaxel

than ddAC followed by paclitaxel (103 [40%] of 260 vs two [1%] of 240); slightly more postmenopausal patients received AC followed by docetaxel (138 [53%] of 260 vs 98 [41%] of 240); and slightly fewer patients with obesity received AC followed by docetaxel (43 [17%] of 260 vs 60 [25%] of 240). In the intravenous infusion group, 120 (48%) of 252 patients received ddAC followed by paclitaxel and 132 (52%) of 252 patients received AC followed by docetaxel. In the fixed-dose combination group, these numbers were 120 (48%) of 248 patients

|                                                   | Intravenous infusion group (n=252) | Fixed-dose combination group (n=248) |
|---------------------------------------------------|------------------------------------|--------------------------------------|
| Age, years                                        | 49.0 (42.0–58.0)                   | 52.0 (44.0–58.5)                     |
| Bodyweight, kg                                    | 66.0 (57.0–76.6)                   | 65.0 (58.0–77.1)                     |
| Ethnic origin                                     |                                    |                                      |
| White                                             | 164 (65%)                          | 165 (67%)                            |
| Asian                                             | 54 (21%)                           | 51 (21%)                             |
| Black or African American                         | 3 (1%)                             | 3 (1%)                               |
| Unknown or other                                  | 31 (12%)                           | 29 (12%)                             |
| ECOG performance status                           |                                    |                                      |
| 0                                                 | 235 (93%)                          | 227 (92%)                            |
| 1                                                 | 16 (6%)                            | 19 (8%)                              |
| Unknown                                           | 1 (<1%)                            | 2 (1%)                               |
| Menopausal status                                 |                                    |                                      |
| Premenopausal                                     | 144 (57%)                          | 118 (48%)                            |
| Postmenopausal                                    | 106 (42%)                          | 130 (52%)                            |
| Unknown                                           | 2 (1%)                             | 0                                    |
| Histological subtype                              |                                    |                                      |
| Invasive carcinoma, no special type               | 194 (77%)                          | 197 (79%)                            |
| Invasive lobular carcinoma                        | 16 (6%)                            | 13 (5%)                              |
| Invasive micropapillary carcinoma                 | 2 (1%)                             | 1 (<1%)                              |
| Mucinous carcinoma                                | 3 (1%)                             | 2 (1%)                               |
| Apocrine carcinoma                                | 3 (1%)                             | 2 (1%)                               |
| Other                                             | 34 (13%)                           | 33 (13%)                             |
| Histological grade                                |                                    |                                      |
| GX                                                | 2 (1%)                             | 4 (2%)                               |
| G1                                                | 9 (4%)                             | 3 (1%)                               |
| G2                                                | 119 (47%)                          | 116 (47%)                            |
| G3                                                | 80 (32%)                           | 90 (36%)                             |
| Unknown                                           | 42 (17%)                           | 35 (14%)                             |
| Hormone receptor status*                          |                                    |                                      |
| Oestrogen and progesterone receptor-negative      | 97 (38%)                           | 96 (39%)                             |
| Oestrogen or progesterone receptor-positive       | 155 (62%)                          | 151 (61%)                            |
| Oestrogen or progesterone receptor status unknown | 0                                  | 1 (<1%)                              |

(Table 1 continues in next column)

|                                  | Intravenous infusion group (n=252) | Fixed-dose combination group (n=248) |
|----------------------------------|------------------------------------|--------------------------------------|
| (Continues from previous column) |                                    |                                      |
| HER2 immunohistochemistry        |                                    |                                      |
| 0                                | 3 (1%)                             | 0                                    |
| 1+                               | 6 (2%)                             | 2 (1%)                               |
| 2+                               | 68 (27%)                           | 74 (30%)                             |
| 3+                               | 175 (69%)                          | 170 (69%)                            |
| Unknown                          | 0                                  | 2 (1%)                               |
| HER2 in-situ hybridisation*      |                                    |                                      |
| Positive                         | 252 (100%)                         | 247 (>99%)                           |
| Negative                         | 0                                  | 1 (<1%)†                             |
| Clinical stage at presentation   |                                    |                                      |
| II–IIIA                          | 202 (80%)                          | 196 (79%)                            |
| IIIB–IIIC                        | 50 (20%)                           | 52 (21%)                             |
| Type of chemotherapy             |                                    |                                      |
| ddAC followed by paclitaxel      | 120 (48%)                          | 120 (48%)                            |
| AC followed by docetaxel         | 132 (52%)                          | 128 (52%)                            |

Data are median (IQR) or n (%). Percentages might not sum to 100% due to rounding. (dd)AC=(dose-dense) doxorubicin plus cyclophosphamide. ECOG=Eastern Cooperative Oncology Group. \*Determined by a central laboratory. †One patient was erroneously centrally assessed as having HER2-positive disease and was randomly assigned to the fixed-dose combination group. The sponsor was notified of this error after the patient had been administered the second chemotherapy cycle; the patient was discontinued from the study and did not receive any HER2-targeted therapy.

**Table 1: Baseline patient demographic and tumour characteristics for the intention-to-treat population**

and 128 (52%) of 248 patients, respectively. 119 (99%) of 120 patients in the intravenous infusion group completed ddAC, 111 (94%) of 118 completed paclitaxel, 130 (98%) of 132 completed AC, and 117 (91%) of 128 completed docetaxel. In the fixed-dose combination group, these numbers were 118 (98%) of 120, 112 (95%) of 118, 126 (98%) of 128, and 113 (90%) of 126, respectively. 241 (96%) of 252 patients completed intravenous pertuzumab, 241 (96%) of 252 completed intravenous trastuzumab, and 234 (94%) of 248 completed the fixed-dose combination during the neo-adjuvant period.

The dose intensity exceeded 98.0% for all drugs in each regimen. Most patients did not experience delays to

chemotherapy: 91 (76%) of 120 in the intravenous infusion group versus 92 (77%) of 120 in the fixed-dose combination group experienced no delays to doxorubicin as part of ddAC; 90 (75%) of 120 versus 93 (78%) of 120, cyclophosphamide as part of ddAC; 71 (60%) of 118 versus 77 (65%) of 118, paclitaxel; 103 (78%) of 132 versus 112 (88%) of 128, doxorubicin as part of AC; 103 (78%) of 132 versus 112 (88%) of 128, cyclophosphamide as part of AC; 101 (79%) of 128 versus 98 (78%) of 126, docetaxel. Most patients did not need at least one chemotherapy dose modification: 113 (94%) of 120 patients in each treatment group for ddAC, 91 (77%) of 118 patients in the intravenous infusion group versus 99 (84%) of 118 patients in the fixed-dose combination group for paclitaxel, 130 (98%) of 132 patients versus 118 (92%) of 128 patients for AC, and 108 (84%) of 128 patients versus 109 (87%) of 126 patients for docetaxel. Most patients did not experience delays to anti-HER2 therapy: 168 (68%) of 247 patients experienced no delay to intravenous pertuzumab, 163 (66%) of 246 patients to intravenous trastuzumab, and 171 (70%) of 243 (70%) to the fixed-dose combination.

473 patients (239 [95%] in the intravenous infusion group and 234 [94%] in the fixed-dose combination group) had a cycle 7 pharmacokinetic measurement. 64 patients (36 in the intravenous infusion group and

|                                                                                                                                                                                                                                                                                                                                                                                | Intravenous infusion group (n=203)   | Fixed-dose combination group (n=206) | GMR (90% CI) or difference (95% CI)* |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| <b>Primary endpoint: cycle 7 (predose cycle 8) pertuzumab serum <math>C_{trough}</math></b>                                                                                                                                                                                                                                                                                    |                                      |                                      |                                      |
| Mean (SD), µg/mL                                                                                                                                                                                                                                                                                                                                                               | 78.5 (26.8)                          | 93.7 (31.5)                          | ..                                   |
| Geometric mean (percentage CV), µg/mL                                                                                                                                                                                                                                                                                                                                          | 72.4 (34.1)                          | 88.7 (33.6)                          | 1.22 (1.14 to 1.31)                  |
| <b>Secondary pharmacokinetic endpoint: cycle 7 (predose cycle 8) trastuzumab serum <math>C_{trough}</math></b>                                                                                                                                                                                                                                                                 |                                      |                                      |                                      |
| Mean (SD), µg/mL                                                                                                                                                                                                                                                                                                                                                               | 47.1 (16.3)                          | 61.6 (22.8)                          | ..                                   |
| Geometric mean (percentage CV), µg/mL                                                                                                                                                                                                                                                                                                                                          | 43.2 (34.7)                          | 57.5 (37.0)                          | 1.33 (1.24 to 1.43)                  |
| <b>Exploratory pharmacokinetic endpoints</b>                                                                                                                                                                                                                                                                                                                                   |                                      |                                      |                                      |
| Cycle 7 (predose cycle 8) pertuzumab serum                                                                                                                                                                                                                                                                                                                                     |                                      |                                      |                                      |
| Mean $C_{max}$ (SD), µg/mL                                                                                                                                                                                                                                                                                                                                                     | 238 (85.0)†                          | 158 (40.1)                           | ..                                   |
| Mean $T_{max}$ (SD), days                                                                                                                                                                                                                                                                                                                                                      | 0.35 (0.82)†                         | 4.35 (2.75)                          | ..                                   |
| Mean AUC <sub>0-21 days</sub> (SD), µg/mL per day                                                                                                                                                                                                                                                                                                                              | 2520 (610)†                          | 2530 (663)                           | ..                                   |
| Geometric mean AUC <sub>0-21 days</sub> (percentage CV), µg/mL per day                                                                                                                                                                                                                                                                                                         | 2440 (28.4)†                         | 2440 (28.0)                          | 1.00 (0.96 to 1.05)                  |
| Cycle 7 (predose cycle 8) trastuzumab serum                                                                                                                                                                                                                                                                                                                                    |                                      |                                      |                                      |
| Mean $C_{max}$ (SD), µg/mL                                                                                                                                                                                                                                                                                                                                                     | 180 (66.7)†                          | 116 (32.4)                           | ..                                   |
| Mean $T_{max}$ (SD), days                                                                                                                                                                                                                                                                                                                                                      | 0.40 (1.66)†                         | 4.45 (2.71)                          | ..                                   |
| Mean AUC <sub>0-21 days</sub> (SD), µg/mL per day                                                                                                                                                                                                                                                                                                                              | 1690 (406)†                          | 1780 (513)                           | ..                                   |
| Geometric mean AUC <sub>0-21 days</sub> (percentage CV), µg/mL per day                                                                                                                                                                                                                                                                                                         | 1640 (27.5)†                         | 1700 (31.2)                          | 1.04 (0.99 to 1.09)                  |
| <b>Pathological complete response endpoint</b>                                                                                                                                                                                                                                                                                                                                 |                                      |                                      |                                      |
| Total pathological complete response in intention-to-treat population                                                                                                                                                                                                                                                                                                          | 150/252 (59.5%, 95% CI 53.2 to 65.6) | 148/248 (59.7%, 95% CI 53.3 to 65.8) | 0.15 (-8.67 to 8.97)                 |
| AUC <sub>0-21 days</sub> =area under the serum concentration-time curve from 0–21 days. $C_{max}$ =maximum serum concentration. $C_{trough}$ =serum trough concentration. CV=coefficient of variation. GMR=geometric mean ratio. $T_{max}$ =time to $C_{max}$ . *Difference (95% CI) is for total pathological complete response in the intention-to-treat population. †n=202. |                                      |                                      |                                      |
| <b>Table 2: Pharmacokinetic parameters in the per-protocol pharmacokinetic population and total pathological complete response in the intention-to-treat population</b>                                                                                                                                                                                                        |                                      |                                      |                                      |

28 in the fixed-dose combination group) were excluded from the primary pharmacokinetic analysis for violations of the protocol; thus, the per-protocol pharmacokinetic population comprised 203 patients in the intravenous infusion group and 206 patients in the fixed-dose combination group.

The GMR of cycle 7 serum pertuzumab  $C_{trough}$  was 1.22 (90% CI 1.14–1.31; table 2; appendix p 11). The GMR of cycle 7 serum trastuzumab  $C_{trough}$  was 1.33 (90% CI 1.24–1.43; table 2). The observed lower limits of the two-sided 90% CIs were above the prespecified non-inferiority margin of 0.8.

Pertuzumab and trastuzumab exposure, as shown by values for serum AUC<sub>0-21 days</sub>, was similar in both treatment groups (table 2). Mean cycle 7 pertuzumab and trastuzumab  $C_{max}$  was higher for intravenous infusion than for the fixed-dose combination (table 2).

Total pathological complete response was achieved by 150 (60%; 95% CI 53–66) of 252 patients in the intravenous infusion group and 148 (60%; 53–66) of 248 patients in the fixed-dose combination group (table 2; appendix p 12). Results from prespecified subgroup analyses are shown in the appendix (pp 13–15).

Post-hoc multiple logistic regression analysis results for total pathological complete response agreed with the unadjusted analyses (appendix p 16).

Clinical response rates were 85% (215 of 252 patients) in the intravenous infusion group and 83% (206 of 248 patients) in the fixed-dose combination group.

A safety overview is given in the appendix (p 17); adverse events occurring in at least 10% of patients at NCI-CTCAE grade 1 or 2, and grade 3 or 4 adverse events occurring in at least 1% of patients are in table 3; and adverse events occurring in at least 10% of patients at NCI-CTCAE grade 1 or 2 and all grade 3, 4, and 5 adverse events are in the appendix (pp 18–21). The most common adverse events (any grade, in >30% of patients) were alopecia (177 [70%] of 252 patients in the intravenous infusion group vs 191 [77%] of 248 patients in the fixed-dose combination group), nausea (152 [60%] vs 146 [59%]), diarrhoea (139 [55%] vs 145 [58%]); the majority of diarrhoea events were low grade and occurred during the first cycle of HER2-targeted treatment), and anaemia (103 [41%] vs 84 [34%]; table 3; appendix pp 18–21). The most common HER2-targeted treatment-related adverse event (any grade, in >30% of patients) in both treatment groups was diarrhoea (82 [33%] of 252 patients in the intravenous infusion group vs 76 [31%] of 248 patients in the fixed-dose combination group). Systemic injection-related or infusion-related reactions related to and occurring within 24 h of HER2-targeted treatment were reported in 26 (10%) of 252 patients in the intravenous

|                                                             | Intravenous infusion group (n=252) |         |         | Fixed-dose combination group (n=248) |         |         |
|-------------------------------------------------------------|------------------------------------|---------|---------|--------------------------------------|---------|---------|
|                                                             | Grade 1 or 2                       | Grade 3 | Grade 4 | Grade 1 or 2                         | Grade 3 | Grade 4 |
| <b>Skin and subcutaneous tissue disorders</b>               |                                    |         |         |                                      |         |         |
| Alopecia                                                    | 177 (70%)                          | 1 (<1%) | 0       | 190 (77%)                            | 1 (<1%) | 0       |
| Rash                                                        | 44 (17%)                           | 0       | 0       | 30 (12%)                             | 1 (<1%) | 0       |
| Dry skin                                                    | 31 (12%)                           | 0       | 0       | 32 (13%)                             | 1 (<1%) | 0       |
| <b>Gastrointestinal disorders</b>                           |                                    |         |         |                                      |         |         |
| Nausea                                                      | 150 (60%)                          | 4 (2%)  | 0       | 142 (57%)                            | 5 (2%)  | 0       |
| Diarrhoea                                                   | 134 (53%)                          | 11 (4%) | 1 (<1%) | 133 (54%)                            | 17 (7%) | 0       |
| Stomatitis                                                  | 58 (23%)                           | 2 (1%)  | 0       | 60 (24%)                             | 2 (1%)  | 0       |
| Constipation                                                | 52 (21%)                           | 0       | 0       | 54 (22%)                             | 0       | 0       |
| Vomiting                                                    | 43 (17%)                           | 3 (1%)  | 0       | 47 (19%)                             | 2 (1%)  | 0       |
| Dyspepsia                                                   | 26 (10%)                           | 0       | 0       | 31 (13%)                             | 0       | 0       |
| <b>General disorders and administration site conditions</b> |                                    |         |         |                                      |         |         |
| Asthenia                                                    | 74 (29%)                           | 5 (2%)  | 0       | 69 (28%)                             | 1 (<1%) | 0       |
| Fatigue                                                     | 55 (22%)                           | 5 (2%)  | 0       | 66 (27%)                             | 5 (2%)  | 0       |
| Mucosal inflammation                                        | 47 (19%)                           | 2 (1%)  | 1 (<1%) | 35 (14%)                             | 2 (1%)  | 0       |
| Pyrexia                                                     | 38 (15%)                           | 1 (<1%) | 0       | 30 (12%)                             | 0       | 0       |
| Injection site reaction                                     | 2 (1%)                             | 0       | 0       | 32 (13%)                             | 0       | 0       |
| <b>Nervous system disorders</b>                             |                                    |         |         |                                      |         |         |
| Headache                                                    | 48 (19%)                           | 2 (1%)  | 0       | 36 (15%)                             | 0       | 0       |
| Dysgeusia                                                   | 35 (14%)                           | 0       | 0       | 41 (17%)                             | 0       | 0       |
| Peripheral sensory neuropathy                               | 34 (13%)                           | 0       | 0       | 36 (15%)                             | 2 (1%)  | 0       |
| Neuropathy peripheral                                       | 28 (11%)                           | 5 (2%)  | 0       | 27 (11%)                             | 1 (<1%) | 0       |
| Syncope                                                     | 1 (<1%)                            | 1 (<1%) | 0       | 1 (<1%)                              | 3 (1%)  | 0       |
| <b>Musculoskeletal and connective tissue disorders</b>      |                                    |         |         |                                      |         |         |
| Myalgia                                                     | 42 (17%)                           | 1 (<1%) | 0       | 52 (21%)                             | 1 (<1%) | 0       |
| Arthralgia                                                  | 44 (17%)                           | 1 (<1%) | 0       | 38 (15%)                             | 0       | 0       |
| <b>Blood and lymphatic system disorders</b>                 |                                    |         |         |                                      |         |         |
| Anaemia                                                     | 96 (38%)                           | 9 (4%)  | 2 (1%)  | 81 (33%)                             | 3 (1%)  | 0       |
| Neutropenia                                                 | 44 (17%)                           | 12 (5%) | 22 (9%) | 26 (10%)                             | 19 (8%) | 16 (6%) |
| Leukopenia                                                  | 31 (12%)                           | 3 (1%)  | 2 (1%)  | 13 (5%)                              | 6 (2%)  | 0       |
| Febrile neutropenia                                         | 0                                  | 11 (4%) | 3 (1%)  | 0                                    | 14 (6%) | 2 (1%)  |
| Lymphopenia                                                 | 5 (2%)                             | 3 (1%)  | 0       | 3 (1%)                               | 1 (<1%) | 0       |
| <b>Investigations</b>                                       |                                    |         |         |                                      |         |         |
| Alanine aminotransferase increased                          | 46 (18%)                           | 3 (1%)  | 0       | 31 (13%)                             | 4 (2%)  | 0       |
| Aspartate aminotransferase increased                        | 36 (14%)                           | 2 (1%)  | 0       | 25 (10%)                             | 2 (1%)  | 0       |
| Neutrophil count decreased†                                 | 34 (13%)                           | 15 (6%) | 16 (6%) | 27 (11%)                             | 10 (4%) | 17 (7%) |
| White blood cell count decreased                            | 23 (9%)                            | 13 (5%) | 5 (2%)  | 16 (6%)                              | 4 (2%)  | 5 (2%)  |
| Lymphocyte count decreased                                  | 3 (1%)                             | 3 (1%)  | 0       | 5 (2%)                               | 3 (1%)  | 0       |
| <b>Respiratory, thoracic, and mediastinal disorders</b>     |                                    |         |         |                                      |         |         |
| Cough                                                       | 30 (12%)                           | 0       | 0       | 32 (13%)                             | 1 (<1%) | 0       |
| Epistaxis                                                   | 34 (13%)                           | 1 (<1%) | 0       | 27 (11%)                             | 0       | 0       |
| Pulmonary embolism                                          | 1 (<1%)                            | 0       | 0       | 0                                    | 2 (1%)  | 1 (<1%) |
| <b>Injury, poisoning, and procedural complications</b>      |                                    |         |         |                                      |         |         |
| Procedural pain                                             | 23 (9%)                            | 0       | 0       | 30 (12%)                             | 0       | 0       |
| Infusion-related reaction                                   | 33 (13%)                           | 2 (1%)  | 0       | 9 (4%)                               | 0       | 0       |
| <b>Metabolism and nutrition disorders</b>                   |                                    |         |         |                                      |         |         |
| Decreased appetite                                          | 46 (18%)                           | 1 (<1%) | 0       | 38 (15%)                             | 2 (1%)  | 0       |
| Hypokalaemia                                                | 18 (7%)                            | 0       | 0       | 11 (4%)                              | 4 (2%)  | 0       |

(Table 3 continues on next page)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Intravenous infusion group (n=252) |         |         | Fixed-dose combination group (n=248) |         |         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|---------|---------|--------------------------------------|---------|---------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Grade 1 or 2                       | Grade 3 | Grade 4 | Grade 1 or 2                         | Grade 3 | Grade 4 |
| (Continued from previous page)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    |         |         |                                      |         |         |
| <b>Vascular disorders</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                    |         |         |                                      |         |         |
| Hot flush                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 26 (10%)                           | 0       | 0       | 19 (8%)                              | 0       | 0       |
| Hypertension                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 3 (1%)                             | 1 (<1%) | 0       | 4 (2%)                               | 5 (2%)  | 0       |
| <b>Psychiatric disorders</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |         |         |                                      |         |         |
| Insomnia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 27 (11%)                           | 1 (<1%) | 0       | 37 (15%)                             | 0       | 0       |
| Data are n (%); patients could be counted in more than one grade category. NCI-CTCAE=US National Cancer Institute Common Terminology Criteria for Adverse Events. *Two deaths occurred (urosepsis in the intravenous infusion group and acute myocardial infarction in the fixed-dose combination group), both assessed by the investigator as unrelated to HER2-targeted therapy. †Differs from neutropenia; definition is a finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen. |                                    |         |         |                                      |         |         |
| <b>Table 3: Adverse events occurring in at least 10% of patients at NCI-CTCAE grade 1 or 2 and grade 3 or 4 adverse events occurring in at least 1% of patients (safety population)*</b>                                                                                                                                                                                                                                                                                                                                                      |                                    |         |         |                                      |         |         |

infusion group and three (1%) of 248 patients in the fixed-dose combination group, most of which were grade 1 or 2 (24 of 26 vs all three). The incidence of systemic reactions within 24 h was highest after the first administration of HER2-targeted treatment and incidence decreased in subsequent administrations. Within the adverse event category of infusion-related and administration-related reactions occurring within 24 h, no patients in the intravenous infusion group reported injection site reactions versus 32 (13%) of 248 patients in the fixed-dose combination group. All were grade 1 or 2 (29 of 32 and three of 32, respectively), with injection site pain and erythema as the most common symptom.

The most common grade 3–4 adverse events occurring in 5% or more of patients were neutropenia (34 [13%] of 252 patients in the intravenous infusion group vs 35 [14%] of 248 in the fixed-dose combination group), decreased neutrophil count (31 [12%] vs 27 [11%]), febrile neutropenia (14 [6%] vs 16 [6%]), diarrhoea (12 [5%] vs 17 [7%]), and decreased white blood cell count (18 [7%] vs nine [4%]). The most common HER2-targeted treatment-related grade 3–4 adverse event was diarrhoea (five [2%] vs nine [4%], respectively).

At least one treatment-related serious adverse event was reported in 25 (10%) patients in the intravenous infusion group and 26 (10%) patients in the fixed-dose combination group. HER2-targeted therapy-related serious adverse events were cardiac failure (two [1%] of 252 patients in the intravenous infusion group and two [1%] of 248 patients in the fixed-dose combination group), infusion-related reactions (two [1%] in the intravenous infusion group only), *Clostridium difficile* colitis, sepsis, urosepsis, and pulmonary embolism in the intravenous infusion group (each in one [<1%] patient), and arrhythmia, colitis, diarrhoea, gastrointestinal toxicity, *Escherichia bacteriaemia*, pneumonitis, and febrile neutropenia in the fixed-dose combination group (each in one [<1%] patient).

One patient in each treatment group had an adverse event that led to death (urosepsis in the intravenous infusion group and acute myocardial infarction in the

fixed-dose combination group; appendix p 17). Neither death was considered to be related to HER2-targeted therapy; the death in the fixed-dose combination group occurred before the start of HER2-targeted therapy.

LVEF was evaluated in all patients at baseline, and in 249 (99%) of 252 patients in the intravenous infusion group and 245 (99%) of 248 patients in the fixed-dose combination group post-baseline. The mean change from baseline to worst LVEF value was  $-5.50\%$  (SD  $5.74$ ) in the intravenous infusion group and  $-5.17\%$  (SD  $5.56$ ) in the fixed-dose combination group (mean difference  $0.3\%$  [95% CI  $-0.7$  to  $1.3$ ]). Seven (3%) patients in the intravenous infusion group and five (2%) in the fixed-dose combination group had at least one clinically significant LVEF drop (of at least 10 ejection fraction points from baseline and to below 50%).

The overall incidence of treatment-emergent anti-drug antibodies was less than 5% in each treatment group (appendix p 22). Exploratory analyses did not suggest that the presence of antidrug antibodies had an adverse effect on total pathological complete response rates or safety (injection-related or infusion-related reactions or administration-related reactions) at clinical cutoff (appendix p 22).

## Discussion

The FeDeriCa primary analysis showed that the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection was non-inferior to intravenous pertuzumab plus trastuzumab, based on cycle 7 pertuzumab and trastuzumab serum  $C_{trough}$  concentrations.

As expected, the pertuzumab and trastuzumab cycle 7  $C_{trough}$  of the fixed-dose combination was higher than that of intravenous pertuzumab plus trastuzumab, with the trastuzumab  $C_{trough}$  GMR similar to that reported in the HannaH study.<sup>9</sup> The overall exposure on the basis of AUC was similar between the fixed-dose combination and intravenous infusions.

All patients in the fixed-dose combination group showed  $C_{trough}$  concentrations above the therapeutic target threshold of 20 µg/mL, which is the effective concentration

identified from mouse xenograft models and early clinical response data,<sup>26</sup> suggesting that the fixed dose was appropriate and ensured adequate receptor saturation.

Efficacy analyses demonstrated that the fixed-dose combination was comparable to intravenous infusions in terms of total pathological complete response, with subgroup analyses generally consistent with the main efficacy results. In particular, there was no discernible association between bodyweight and total pathological complete response. Multiple logistic regression analyses were mostly in line with the corresponding unadjusted results. In addition, total pathological complete response rates were consistent with the results from other trials with intravenous pertuzumab plus trastuzumab in patients with HER2-positive breast cancer, in which intravenous pertuzumab plus trastuzumab was given in combination with an anthracycline-based or a taxane-based regimen before surgery with rates of total pathological complete response ranging from 54% to 64%.<sup>27–30</sup> Recent studies have reported no increased benefit of adjuvant ddAC in HER2-positive disease;<sup>31,32</sup> however, patients who received ddAC followed by paclitaxel appeared to have numerically greater total pathological complete response rates in FeDeriCa than those who received AC followed by docetaxel. In our study, the chemotherapy choice seemed to be dependent on the region (eg, the higher AC followed by docetaxel numbers were in Asian patients). The differences in total pathological complete response between chemotherapy type are most likely a chance finding.

Approximately half the patients in each treatment group had grade 3–5 adverse events, and this did not result in premature withdrawal from HER2-targeted therapy, as evidenced by the high number of patients who completed neoadjuvant treatment at the time of clinical cutoff (which itself indicates good tolerability).

The overall safety profile of the fixed-dose combination was similar to that of intravenous infusions, with the exception of adverse events related to the different routes of administration (ie, injection site reactions). No new or unexpected toxicities were observed. As expected, the most common grade 3–4 adverse events with the fixed-dose combination were neutropenia, decreased neutrophil count, febrile neutropenia, diarrhoea, and decreased white blood cell count. Diarrhoea rarely led to discontinuation. Local injection site reactions reported in the fixed-dose combination group were infrequent and all low grade, and rates are in line with injection site reactions reported with subcutaneous trastuzumab.<sup>9</sup> By contrast, systemic infusion-related reactions were more frequent in the intravenous infusion group. This numerical difference might be attributable to differences in systemic absorption and the low  $C_{max}$  related to subcutaneous administration (the mean cycle 7  $C_{max}$  for pertuzumab and trastuzumab in the fixed-dose combination group were lower than in the intravenous infusion group).

The incidence of primary and secondary cardiac events was low in both treatment groups with no meaningful difference, and consistent with rates reported in previous studies with similar chemotherapy regimens.<sup>27</sup> The extent and proportion of patients with changes in LVEF were also similar in the two treatment groups. The only cardiac death was reported in the fixed-dose combination group, although it occurred during treatment with anthracyclines and before the start of the HER2-targeted therapy. None of the fatal events was related to HER2 treatment.

Immunogenicity analyses showed that the incidence of antidrug antibodies in the fixed-dose combination group was low, comparable to that in the intravenous infusion group, and did not appear to have any adverse clinical consequences with respect to pharmacokinetics, efficacy, and safety.

Overall, the efficacy and safety data for the fixed-dose combination plus chemotherapy from this study were consistent with the known efficacy and safety profile of pertuzumab plus trastuzumab plus chemotherapy in patients with HER2-positive breast cancer.<sup>27–30</sup>

This current analysis has some limitations. The primary analysis was done after completion of the neoadjuvant phase; however, HER2-targeted treatment is continuing up to 18 cycles, as per standard of care. Therefore, safety, efficacy, and pharmacokinetic results from the adjuvant phase and 3-year end of follow-up results are not yet available. However, the long-term safety and efficacy profile of the fixed-dose combination in FeDeriCa is expected to be similar to that of intravenous infusions. No chemotherapy was administered in the adjuvant setting in FeDeriCa; hence, safety is not expected to worsen during longer follow-up based on the large body of evidence regarding the pattern and incidence of adverse events, which are most frequently reported when intravenous pertuzumab plus trastuzumab is given concomitantly with chemotherapy. Long-term efficacy results of the HannaH study support the established non-inferiority of subcutaneous trastuzumab versus intravenous trastuzumab, and the safety profile remained consistent with that of intravenous administration over time.<sup>11</sup> In addition, the final results from the MetaPHER study (a single-arm, phase 3 study assessing the safety of subcutaneous trastuzumab in combination with intravenous pertuzumab and docetaxel in patients with previously untreated advanced breast cancer) demonstrated that the safety, including long-term safety, of this regimen was similar to historical data from intravenous pertuzumab plus trastuzumab and docetaxel in patients with HER2-positive advanced breast cancer.<sup>19</sup> At a follow-up of 26·7 months (maximum 45 months) in MetaPHER, no cumulative toxicity or late cardiac safety issues were observed with subcutaneous trastuzumab.

The shorter duration of administration of the fixed-dose combination than of intravenous infusions has the potential to provide substantial time saving for patients,

physicians, nurses, and pharmacy staff. Based on the positive experience with subcutaneous trastuzumab home administration,<sup>33</sup> the fixed-dose combination also has the potential to be administered at home, as approved by the FDA.

An oncology hospital-at-home programme in the USA reported reduced hospitalisations, emergency department visits, and costs versus standard care processes.<sup>34</sup> A UK analysis of care in the home for patients with cancer or chronic conditions, and those needing end-of-life care, suggested that the benefits of home treatment extend to better adherence, ability to resume or continue daily activities (ie, re-enablement), improved quality of life, patient activation, and financial savings.<sup>35</sup> Optimisation efforts are ongoing for other agents, including cancer immunotherapies.<sup>36</sup>

Investigation of patient preference and satisfaction and safety of switching between formulations, as well as health-care professionals' perceptions of time and resource use and convenience related to the fixed-dose combination as compared with intravenous infusions, are currently being assessed in the crossover, phase 2 PHranceSCa trial (NCT03674112). The primary analysis showed that most (136 [85%] of 160) patients preferred the fixed-dose combination to intravenous infusions and that 87% of patients chose the fixed-dose combination to complete their 18 cycles of treatment after experiencing both methods. It also showed that the fixed-dose combination was generally well tolerated, even when switching between formulations.<sup>37</sup> This is despite the fixed-dose combination being more viscous with a relatively high injection volume.

In conclusion, the non-inferior cycle 7 pertuzumab and trastuzumab  $C_{trough}$  of the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection to intravenous pertuzumab plus trastuzumab, the comparable total pathological complete response rates, and the comparable safety profiles (including cardiac safety) support the recent approval by the FDA. Follow-up is ongoing for long-term outcomes, including efficacy and long-term safety.

#### Contributors

ART contributed to the study design and collection and assembly of data. S-AI contributed to protocol development, study design, data collection, and patient enrolment. AM contributed to study design, data collection, and patient recruitment. RC contributed to protocol development, study design, and data collection. ZN, KHJ, and CS contributed to data collection. AH contributed to data analysis. TBC and SH contributed to study design and data collection. MS contributed to study design and statistical analysis. WPK contributed to study design, data collection, and data analysis. ER contributed to the study design and figures. CJ contributed to study design, writing of the protocol, data collection, and patient enrolment. All authors reviewed the data analyses, contributed to data interpretation, contributed to drafting or revision of the manuscript for important intellectual content, approved the final version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

#### Declaration of interests

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#### Data sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform. Further details on Roche's criteria for eligible studies are available online. Further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents are available online.

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