Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial

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Summary

Background HER2-targeted treatments have improved outcomes in patients with HER2-positive breast cancer in the neoadjuvant, adjuvant, and metastatic settings; however, some patients remain at risk of relapse or death for many years after treatment of early-stage disease. Therefore, new strategies are needed. We did a phase 3 trial to assess a neoadjuvant regimen for HER2-positive breast cancer that replaces traditional systemic chemotherapy with targeted treatment.

Methods We did a randomised, open-label phase 3 KRISTINE trial in 68 Translational Research In Oncology centres (hospitals and specialty cancer centres in Asia, Europe, USA, and Canada). Eligible participants were aged 18 years or older with centrally confirmed HER2-positive stage II–III operable breast cancer (>2 cm tumour size), an Eastern Cooperative Oncology Group performance status of 0–1, and a baseline left ventricular ejection fraction of at least 55% (by echocardiogram or multiple-gated acquisition scan). We randomly assigned participants (1:1) to receive either trastuzumab emtansine plus pertuzumab or docetaxel, carboplatin, and trastuzumab plus pertuzumab. We did the randomisation via an interactive response system under a permuted block randomisation scheme (block size of four), stratified by hormone receptor status, stage at diagnosis, and geographical location. Patients received six cycles (every 3 weeks) of neoadjuvant trastuzumab emtansine plus pertuzumab (trastuzumab emtansine 3·6 mg/kg; pertuzumab 840 mg loading dose, 420 mg maintenance doses) or docetaxel, carboplatin, and trastuzumab plus pertuzumab (docetaxel 75 mg/m²; carboplatin area under the concentration–time curve 6 mg/mL × min; trastuzumab 8 mg/kg loading dose, 6 mg/kg maintenance doses) plus pertuzumab [same dosing as in the other group]). All treatments were administered intravenously. The primary objective was to compare the number of patients who achieved a pathological complete response (ypT0/is, ypN0), between groups in the intention-to-treat population (two-sided assessment), based on local evaluation of tumour samples taken at breast cancer surgery done between 14 days and 6 weeks after completion of neoadjuvant therapy. Safety was analysed in patients who received at least one dose of study medication. This trial is registered with ClinicalTrials.gov, number NCT02131064, and follow-up of the adjuvant phase is ongoing.

Findings Between June 25, 2014, and June 15, 2015, we randomly assigned 444 patients to neoadjuvant treatment with trastuzumab emtansine plus pertuzumab (n=223) or docetaxel, carboplatin, and trastuzumab plus pertuzumab (n=221). A pathological complete response was achieved by 99 (44·4%) of 223 patients in the trastuzumab emtansine plus pertuzumab group and 123 (55·7%) of 221 patients in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group (absolute difference −11·3 percentage points, 95% CI −20·5 to −2·0; p=0·016). During neoadjuvant treatment, compared with patients receiving docetaxel, carboplatin, and trastuzumab plus pertuzumab, fewer patients receiving trastuzumab emtansine plus pertuzumab had a grade 3–4 adverse event (29 [13%] of 223 *vs* 141 [64%] of 219) or a serious adverse event (11 [5%] of 223 *vs* 63 [29%] of 219). The most common grade 3–4 adverse events in the trastuzumab emtansine plus pertuzumab group were decreased platelet count (three [1%] of 223 patients vs 11 [5%] of 219 with docetaxel, carboplatin, and trastuzumab plus pertuzumab), fatigue (three [1%] *vs* seven [3%]), alanine aminotransferase increase (three [1%] *vs* four [2%]), and hypokalaemia (three [1%] *vs* five [2%]). The most common grade 3–4 adverse events in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group were neutropenia (55 [25%] of 219 *vs* one [<1%] of 223 with trastuzumab emtansine plus pertuzumab), diarrhoea (33 [15%] *vs* 2 [<1%]), and febrile neutropenia (33 [15%] *vs* 0). No deaths were reported during neoadjuvant treatment.

Interpretation Traditional neoadjuvant systemic chemotherapy plus dual HER2-targeted blockade (docetaxel, carboplatin, and trastuzumab plus pertuzumab) resulted in significantly more patients achieving a pathological complete response than HER2-targeted chemotherapy plus HER2-targeted blockade (trastuzumab emtansine plus

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pertuzumab); however, numerically more grade 3–4 and serious adverse events occurred in the chemotherapy plus trastuzumab and pertuzumab group. Further efforts to improve the efficacy of chemotherapy without imparting more toxicity are warranted.

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Introduction

In the neoadjuvant setting, use of trastuzumab-based regimens for HER2-positive breast cancer has resulted in 39–45% of patients achieving a pathological complete response,[1–3] although proportions of as low as 25% and as high as 65% have also been reported.[4,5] Despite the improvements in outcomes associated with HER2-directed therapy, approximately a quarter of patients who receive treatment for their early breast cancer remain at risk of relapse after 8–10 years,[6–8] and around 15% will die within a decade.[6,8] Findings from previous studies have shown that dual-agent HER2 blockade increases the number of patients achieving a pathological complete response compared with single-agent HER2-directed treatment, without notably affecting safety.[9,10] In the NeoSphere trial,[9] the addition of pertuzumab—a HER2-directed monoclonal antibody—to neoadjuvant trastuzumab plus docetaxel significantly increased the proportion of patients achieving a pathological complete response compared with trastuzumab plus docetaxel, leading to the approval of neoadjuvant trastuzumab and pertuzumab plus taxane chemotherapy in the USA, European Union, and other regions. Trastuzumab emtansine is an antibody–drug conjugate that has led to improved overall survival in patients with HER2-positive metastatic breast cancer, who were previously treated with trastuzumab and a taxane, in two randomised phase 3 trials.[11,12] Trastuzumab emtansine is not associated with typical chemotherapy side-effects because of the targeted delivery of the chemotherapy to HER2-overexpressing cells.

Early breast cancer generally has 10-year survival rates of approximately 89% for patients with local disease and 62% for patients with regional involvement.[13] In patients with HER2-positive early breast cancer, however, incorporation of highly effective anti-HER2 therapies has led to 3-year survival rates in excess of 90%.[14] We therefore did a phase 3 trial comparing trastuzumab emtansine plus pertuzumab—a regimen that does not contain

Research in context

Evidence before this study

We searched PubMed for clinical trials assessing HER2-targeted therapeutic interventions for patients with HER2-positive early breast cancer published between Jan 1, 2000, and Jan 31, 2014. Search terms were "early breast cancer", "HER2-positive", "neoadjuvant", "pertuzumab", "lapatinib", and "trastuzumab". Our findings indicated that outcomes in patients with HER2-positive early breast cancer were improved by combining chemotherapy with a HER2-directed drug in the neoadjuvant setting. However, despite this improved activity, a substantial number of patients still had residual disease (rather than achieving a pathological complete response) at surgery. The evidence also showed that using a combination of two HER2-targeted therapies with complementary mechanisms of action (eg, pertuzumab and trastuzumab, or trastuzumab and lapatinib) improved the proportion of patients achieving a pathological complete response when used with chemotherapy, and that dual blockade HER2-directed therapy showed efficacy when used without chemotherapy. Therefore, we designed a study to assess HER2-targeted therapy (trastuzumab emtansine) plus pertuzumab, to see if this combination could increase the number of patients achieving a pathological complete response significantly more than previously observed with a combination of HER2-targeted therapies that did not have directed delivery of a cytotoxic agent. Our choice of control group was docetaxel, carboplatin, and trastuzumab plus pertuzumab, selected on the evidence-based assumption that dual blockade HER2-directed therapy combined with chemotherapy would ultimately become a global therapeutic approach in the neoadjuvant setting.

Added value of this study

To our knowledge, the KRISTINE study was the first phase 3 trial to compare a neoadjuvant regimen for HER2-positive breast cancer that excluded traditional systemic chemotherapy and replaced it with targeted chemotherapy. The study confirmed that in patients with HER2-positive stage II–III breast cancer, neoadjuvant docetaxel, carboplatin, and trastuzumab plus pertuzumab was associated with a larger proportion of patients achieving a pathological complete response and numerically more patients receiving breast-conserving surgery than was trastuzumab emtansine plus pertuzumab. However, compared with the chemotherapy-based regimen, trastuzumab emtansine plus pertuzumab was associated with fewer adverse events of grade 3–4 and serious adverse events, and longer maintenance of patient-reported health-related quality of life and physical function.

Implications of all the available evidence

In the neoadjuvant setting, patients are treated with curative intent. Currently, the standard therapeutic approach to optimising the number of patients with HER2-positive early breast cancer achieving a pathological complete response remains HER2 blockade plus traditional chemotherapy. Thus, our results support neoadjuvant docetaxel, carboplatin, and trastuzumab plus pertuzumab remaining the standard of care.

traditional systemic chemotherapy—with a docetaxel, carboplatin, and trastuzumab plus pertuzumab regimen in patients with HER2-positive early-stage (stage II–III) breast cancer.

Methods

Study design and participants

We did a randomised, multicentre, open-label, phase 3 study (KRISTINE) at 68 Translational Research In Oncology centres (hospitals and specialty cancer centres) in ten countries in Asia, Europe, USA, and Canada (appendix pp 7–8). This report summarises efficacy, safety, and patient-reported outcome data from the neoadjuvant phase of the trial. Adjuvant treatment ended in November, 2016, and follow-up in the adjuvant phase is ongoing.

Eligible patients were women and men aged at least 18 years with operable, clinical stage cT2–cT4/cN0–cN3/cM0 (stage II–III) breast cancer (>2 cm in size) centrally confirmed as HER2-positive from protein overexpression (immunohistochemistry 3+ [PATHWAY anti-HER-2/neu (4B5) assay, Ventana Medical Systems, Tucson, AZ, USA) or gene amplification (in-situ hybridisation positive [INFORM HER2 Dual ISH assay, Ventana Medical Systems]). The hormone receptor status (oestrogen receptor and progesterone receptor status) of the patients' primary tumour had to be known. Participants were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and baseline left ventricular ejection fraction (LVEF) of at least 55% (as measured by echocardiogram or multiple-gated acquisition scan). Participants were also required to have adequate organ function based on laboratory assessment of absolute neutrophil count, platelet count, haemoglobin, serum creatinine, international normalised ratio and (activated) partial thromboplastin time, aspartate transaminase (AST) and alanine transaminase (ALT), serum total bilirubin, and serum alkaline phosphatase. Exclusion criteria included bilateral or multicentric breast cancer (multiple tumours involving >1 quadrant), stage IV (metastatic) breast cancer, a history of invasive breast cancer, previous systemic therapy for the treatment or prevention of breast cancer, or previous incisional or excisional biopsy of a primary tumour or axillary lymph node. Patients were also excluded if they had a positive sentinel lymph node biopsy at baseline, cardiopulmonary dysfunction, a notable concurrent medical or surgical condition, peripheral neuropathy of grade 2 or worse (as per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.0), or had received treatment with any investigational drug within 28 days before randomisation.

The KRISTINE trial is being conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. Ethics approval was obtained from the institutional review board or ethics committee at each participating site. All patients provided written informed consent.

Randomisation and masking

We randomly assigned patients (1:1) via an interactive web-based response system (S-Clinica, Brussels, Belgium) to receive either trastuzumab emtansine plus pertuzumab or docetaxel, carboplatin, and trastuzumab plus pertuzumab under a permuted block randomisation scheme (block size of four). Randomisation was stratified by local assessment of hormone receptor status (oestrogen-receptor-positive or progesterone-receptor-positive, or both *vs* oestrogen-receptor-negative and progesterone-receptor-negative), clinical stage at presentation (II–IIIA *vs* IIIB–IIIC), and geographical location (North America *vs* western Europe *vs* rest of the world). As this was an open-label study, patients, investigators, and the study team were not masked to study treatment.

See Online for appendix

Procedures

Patients assigned to trastuzumab emtansine plus pertuzumab received trastuzumab emtansine (3·6 mg/kg, given intravenously over 90 min for the first dose and over 30–90 min for subsequent doses) and pertuzumab (840 mg loading dose given intravenously over 60 min, 420 mg maintenance doses given intravenously over 30–60 min). Patients assigned to docetaxel, carboplatin, and trastuzumab plus pertuzumab received docetaxel (75 mg/m² intravenously over 60 min), carboplatin (area under the concentration–time curve [AUC] 6 mg/mL×min intravenously over 30–60 min), trastuzumab (8 mg/kg loading dose intravenously over 90 min, 6 mg/kg maintenance doses over 30–90 min), and pertuzumab (same dosing as in the other group). Treatments were administered in 21-day cycles (plus or minus 3 days). In both treatment groups, patients received a total of six cycles in the neoadjuvant phase, and HER2-directed therapy (ie, trastuzumab emtansine, pertuzumab, and trastuzumab). All study drugs were administered intravenously. Dose reductions were not permitted for trastuzumab or pertuzumab; however, dose delays of up to 42 days for these drugs were permitted for selected adverse events such as grade 2 or 3 infusion-related reactions, grade 2–4 thrombocytopenia, cardiovascular events identified on echocardiogram or multiple-gated acquisition scan, or other clinically significant adverse events (full list in protocol, appendix p 12). Dose reductions or delays were allowed for trastuzumab emtansine, docetaxel, or carboplatin in the event of toxicity, such as grade 2–3 hepatotoxicity, grade 2–4 thrombocytopenia, any grade of pneumonitis, or other clinically significant adverse events (full list in protocol, appendix p 12) and were done according to specified dose-reduction levels. Dose re-escalation was not permitted. For trastuzumab emtansine, the dose was first reduced to 3 mg/kg then to

2·4 mg/kg; after this reduction trastuzumab emtansine was discontinued. For docetaxel, the first dose reduction was to 60 mg/m² and the next to 50 mg/m², after which docetaxel was discontinued. For carboplatin, the first dose reduction was to an AUC of 5 mg/mL×min then to 4 mg/mL×min, after which carboplatin was discontinued. If administration of trastuzumab emtansine, docetaxel, or carboplatin was delayed, administration of the other drugs was also delayed. However, if trastuzumab or pertuzumab were delayed, administration of the other drugs could continue. Use of growth factors such as filgrastim, pegfilgrastim, lenograstim, or others in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group was recommended for primary prophylaxis of treatment-emergent neutropenia; growth factor use was also permitted for secondary prophylaxis of treatment-emergent neutropenia in both treatment groups and was used at the investigator's discretion. Patients remained in study follow-up, irrespective of whether or not they remained on study treatment, unless consent was withdrawn.

Patients underwent tumour staging and bilateral mammogram at screening and had ultrasounds at screening and before definitive breast cancer surgery. Subsequent mammograms were optional during neoadjuvant treatment and before surgery, and were done at the investigator's discretion. Additional breast imaging could be done at the investigator's discretion, but were not required. Assessment of the primary tumour and regional lymph nodes was done by physical examination at baseline and before administration of each cycle of study treatment during neoadjuvant therapy. Additional investigations such as bone scans, chest radiograph or diagnostic CT scans, liver imaging, or other radiographic modalities were considered when clinically indicated to exclude metastatic disease; these assessments were done according to local standards of practice. Laboratory monitoring, including assessment of haematology and serum chemistries, was completed before administration of each cycle of study treatment. Adverse events were assessed with each cycle of study drug and all adverse events (based on NCI CTCAE, version 4.0) were reported through 28 days after the last dose of study drug.

Between 14 days and 6 weeks after the last dose of neoadjuvant therapy, patients underwent definitive breast cancer surgery. Within 9 weeks of surgery, patients resumed the HER2-targeted regimen to which they had been randomly assigned in the neoadjuvant phase (trastuzumab emtansine plus pertuzumab or trastuzumab plus pertuzumab) for 12 cycles. Thus, patients received a total of 18 cycles of HER2-directed therapy. Adjuvant radiotherapy was given as clinically indicated, and patients with tumours that were oestrogen-receptor-positive, progesterone-receptor-positive or both received adjuvant endocrine therapy. Because adjuvant endocrine therapy was administered according to local practice, specific treatments were not specified in the study protocol. Additional chemotherapy was not recommended for patients with residual disease who had received neoadjuvant docetaxel, carboplatin, and trastuzumab plus pertuzumab because there was no established role for additional chemotherapy after surgery, even for patients who did not achieve a pathological complete response. Only patients assigned to trastuzumab emtansine plus pertuzumab who did not achieve a pathological complete response and who had residual tumour larger than 1 cm or residual nodal disease (>ypN0) were recommended for anthracycline-based chemotherapy (≥4 cycles), which was administered at the discretion of the treating physician before resuming study HER2-targeted therapy.

Tumour samples were taken at surgery following the completion of neoadjuvant therapy and assessed by local pathology review. Consistent with the American Joint Committee on Cancer staging system,[15] the primary endpoint of pathological complete response (ypT0/is, ypN0) was defined as the absence of any residual invasive cancer on haematoxylin and eosin staining of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of systemic neoadjuvant therapy. Local training and reporting of this endpoint were standardised via the implementation of a study pathology manual and audio-visual pathology training, which involved live and virtual training by members of a global breast pathology expert panel. Members of this expert panel were also available at individual sites for consultation regarding assessments of pathological complete response.

Outcomes

The primary efficacy endpoint was locally determined pathological complete response (ypT0/is, ypN0). Prespecified subgroup analyses of pathological complete response were also done. Protocol-defined secondary endpoints were the proportion of patients without inflammatory breast cancer who had breast-conserving surgery, patient-reported outcomes related to quality of life, and safety assessments. For patient-reported outcomes, global health status or health-related quality of life (HRQOL) and physical functioning were assessed during the neoadjuvant phase using the European Organisation for Research and Treatment of Cancer quality of life questionnaire (QLQ)-C30 and QLQ-modified breast cancer module (BR23).[16,17] Additional protocol-specified secondary endpoints were event-free survival (time from randomisation to disease progression, disease recurrence, or death from any cause), invasive disease-free survival (time from surgery to the first documented occurrence of an event such as ipsilateral invasive breast tumour recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause), and overall survival (time from randomisation to death from any cause).

Pharmacokinetics were also assessed in this study (protocol, appendix p 12), but are not part of this report. Results for event-free survival, invasive disease-free survival, and overall survival including the number of events that have occurred and median follow-up, are also not in this report. These endpoints, as well as the number of patients with residual disease, will only be analysed as part of the adjuvant phase of the trial after a median follow-up of approximately 36 months. Additional analyses of quality-of-life data from the QLQ-C30 and QLQ-modified BR23 from the adjuvant phase are also planned.

The safety outcome measures included the incidence, type, and severity of all adverse events (including serious adverse events) based on NCI CTCAE version 4.0, and the incidence and type of adverse events leading to dose discontinuation, modification, or delay. Additional safety outcome measures were hepatic events (defined as death from hepatic cause, severe drug-induced liver injury, confirmed Hy's law cases, or nodular regenerative hyperplasia), and cardiac events (defined as death from cardiac cause or severe congestive heart failure [New York Heart Association Class III or IV] with a decrease in LVEF of ≥10 percentage points from baseline to an LVEF of ≤50%). The proportion of patients with conversion to breast-conserving surgery, defined as the proportion of patients originally deemed to require masectomy, but who were then considered eligible for breast-conserving surgery after neoadjuvant therapy, was a prespecified exploratory endpoint. Additional exploratory analyses were completed such as evaluation of biomarkers, the residual cancer burden index, and different definitions of pathological complete response (complete list in protocol, appendix p 12); however, these analyses are not included in this report.

Statistical analysis

With 216 patients enrolled per treatment group, the study had 90% power to detect an increase in the proportion of patients with a pathological complete response from 60% (assumed for docetaxel, carboplatin, and trastuzumab plus pertuzumab) to 75% (assumed for trastuzumab emtansine plus pertuzumab), at a two-sided α level of 5%. The primary efficacy endpoint of the proportion of patients who achieved a pathological complete response was analysed in the intention-to-treat population (all randomly assigned patients irrespective of whether or not they received study treatment, analysed according to their randomly assigned treatment) and compared between treatment groups using the Cochran-Mantel-Haenszel χ^2 test[18] (stratified by local hormone receptor status and clinical stage at presentation). We used the Blyth-Still-Casella[19,20] method to calculate the corresponding 95% CIs in each treatment group. The 95% CIs for the between-group difference were derived using a normal approximation. Patients without a reported assessment of pathological complete response (eg, those with disease progression or toxicity before surgery) were categorised as not having achieved a pathological complete response. We did an exploratory multivariate logistic regression analysis to assess covariates that might have been related to pathological complete response.

The proportion of patients who received breast-conserving surgery (with 95% CIs)[19,20] was calculated for each treatment group. Patient-reported outcomes collected during the neoadjuvant phase were analysed for all patients with a baseline assessment and at least one post-baseline assessment. Maintenance of HRQOL and physical function were assessed as the time to deterioration, which was defined as the time from baseline to the first decrease of at least ten percentage points. Patients were considered having a decrease of at least 10 points relative to baseline if at any post baseline assessment, a decrease of 10 or more points were observed. Questionnaire assessments like HRQOL

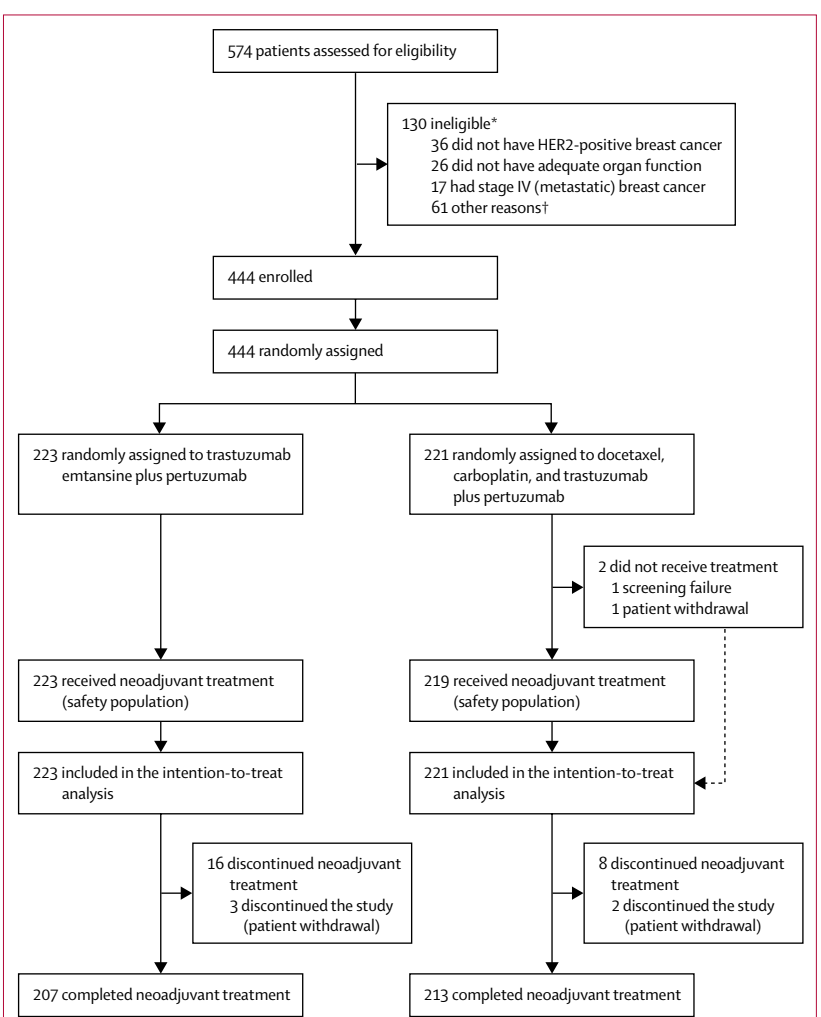

Figure 1: **Trial profile**
*Patients could have had multiple reasons for screening failure. †Includes non-compliance with study protocol, use of pertuzumab as a single agent, and others.

	Trastuzumab emtansine plus pertuzumab (n=223)	Docetaxel, carboplatin, and trastuzumab plus pertuzumab (n=221)
Sex		
Female	222 (>99%)	221 (100%)
Male	1 (<1%)	0
Age, years	50 (42–57)	49 (41–57)
World region		
North America	54 (24%)	54 (24%)
Western Europe	85 (38%)	84 (38%)
Rest of world	84 (38%)	83 (38%)
Local oestrogen-receptor or progesterone-receptor status		
Oestrogen-receptor-negative and progesterone-receptor-negative	84 (38%)	83 (38%)
Oestrogen-receptor-positive or progesterone receptor-positive	139 (62%)	138 (62%)
Clinical stage at presentation		
IIA–IIIA	186 (83%)	183 (83%)
IIIB–IIIC	37 (17%)	38 (17%)
Race		
White	148 (66%)	147 (67%)
Black	5 (2%)	6 (3%)
Asian	60 (27%)	52 (24%)
Other*	10 (4%)	16 (7%)
ECOG performance status		
0	209 (94%)	212 (96%)
1	14 (6%)	9 (4%)
Median time from breast cancer diagnosis, weeks	5·0 (4·0–6·3)	5·3 (4·1–7·0)

Data are n (%) or median (IQR). Some percentages do not add up to 100% because of rounding. ECOG=Eastern Cooperative Oncology Group. *Includes American Indian or Alaska Native, Native Hawaiian, or other Pacific Islander, multiple, and not available.

Table 1: **Baseline characteristics of the intention-to-treat population**

were done at baseline, cycle 3 day 1, cycle 5 day 1, and pre-surgery.

Safety data were analysed descriptively in all patients who received at least one full or partial dose of study medication; patients were analysed on the basis of the treatment they received. An independent data monitoring committee monitored data on serious adverse events and deaths at least once every 3 months, and accumulated patient safety data at least once every 6 months until the primary endpoint was reached. Statistical analyses were done using SAS versions 9.2 and 9.4. This trial is registered with ClinicalTrials.gov, number NCT02131064.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author prepared the initial draft of the report, with support from a medical writer paid by the funder. All authors had full access to all the data in the study, were involved in data analysis and interpretation, contributed to subsequent manuscript drafts, and had final responsibility for the decision to submit for publication.

Results

Between June 25, 2014, and June 15, 2015, we screened 574 patients and randomly assigned 444 to the two treatment groups: 223 to trastuzumab emtansine plus pertuzumab and 221 to docetaxel, carboplatin, and trastuzumab plus pertuzumab (figure 1). The most common reason for screening failure was not meeting the inclusion criterion of HER2-positive breast cancer. 442 patients received at least one dose of study treatment; two patients randomly assigned to docetaxel, carboplatin, and trastuzumab plus pertuzumab did not receive study drug (figure 1). Baseline characteristics were well balanced between the treatment groups (table 1). The clinical data cutoff date for the present analysis, which followed the last pathological assessment of pathological complete response, was Dec 3, 2015. The database extract was taken on Feb 22, 2017, then all data were cut back to the clinical cutoff date.

A pathological complete response was achieved by 99 (44%) of 223 patients in the trastuzumab emtansine plus pertuzumab group and 123 (56%) of 221 patients in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group (absolute difference −11·3 percentage points, 95% CI −20·5 to −2·0; p=0·016; figures 2, 3). 18 (8%) patients assigned to trastuzumab emtansine plus pertuzumab and seven (3%) assigned to docetaxel, carboplatin, and trastuzumab plus pertuzumab did not have an assessment of pathological complete response because of disease progression or early discontinuation and were categorised as not achieving a pathological complete response. Subgroup analyses of pathological complete response by treatment in subgroups defined by clinically relevant baseline characteristics are shown in figures 2 and 3. In an exploratory multivariate logistic regression analysis to control for clinicopathological factors, treatment with trastuzumab emtansine plus pertuzumab and positive local hormone receptor status were associated with lower odds of achieving a pathological complete response (odds ratios 0·62, 95% CI 0·42–0·93 and 0·43, 0·28–0·65, respectively, with docetaxel, carboplatin, and trastuzumab plus pertuzumab pertuzumab and negative local hormone receptor status used as a reference; appendix p 4).

In the subset of patients without inflammatory breast cancer (n=431), breast-conserving surgery was done in 91 (42%) of 218 patients assigned to trastuzumab emtansine plus pertuzumab and 112 (53%) of 213 assigned to docetaxel, carboplatin, and trastuzumab plus pertuzumab (absolute difference −10·8 percentage points, 95% CI −20·2 to −1·5). Of 207 patients originally deemed by the local investigator to require mastectomy, conversion to eligibility for breast-conserving surgery after neoadjuvant treatment was achieved by 71 (66%) of 108 patients assigned to trastuzumab emtansine plus pertuzumab and 66 (70%) of 99 of those assigned to docetaxel, carboplatin, and trastuzumab plus pertuzumab

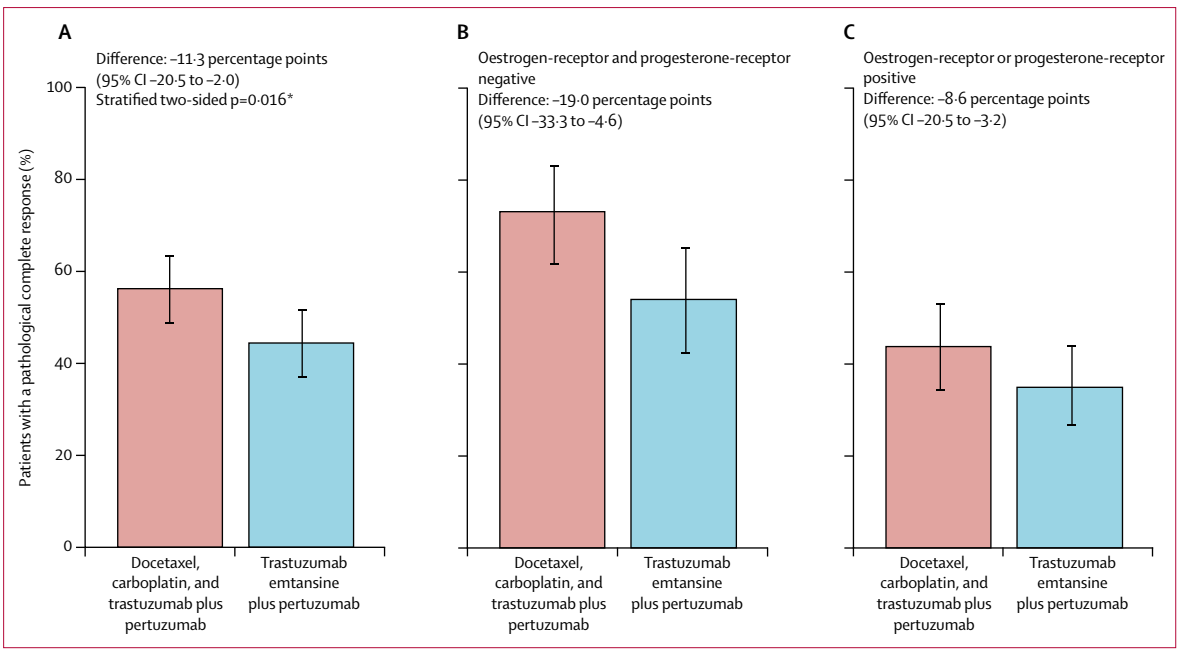

Figure 2: **Pathological complete response**
Data are percentage points (95% CI) for A, overall pathological complete response (ypT0/is, ypNo) and (B) and (C) pathological complete response by central hormone receptor status. Patients with missing or unevaluable pathological complete response status were considered non-responders. Some percentages do not add up to 100% because of rounding. 20 patients (11 in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group and nine in the trastuzumab emtansine plus pertuzumab group) had an unknown oestrogen receptor or progesterone receptor status by central analysis and are therefore not included in the analysis of pathological complete response by central hormone receptor status. *Cochran-Mantel-Haenszel χ^2 p value.

(absolute difference: –4·0 percentage points, 95% CI –16·7 to 8·8; appendix p 2).

Median time to deterioration in HRQOL was 4·6 months (95% CI 4·1–8·0) in the trastuzumab emtansine plus pertuzumab group and 3·0 months (2·8–3·4) in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group (appendix p 3). Median time to deterioration in physical function was 4·9 months (95% CI 4·4–8·0) with trastuzumab emtansine plus pertuzumab versus 2·8 months (2·8–3·0) with docetaxel, carboplatin, and trastuzumab plus pertuzumab (appendix p 3). Relative to baseline, a decrease of at least 10 points in HRQOL occurred at any post-baseline assessment in 92 (46%) of 200 patients assigned to trastuzumab emtansine plus pertuzumab and in 134 (70%) of 191 assigned to docetaxel, carboplatin, and trastuzumab plus pertuzumab. Corresponding patient numbers for a decrease of at least 10 points in physical function were 81 (41%) of 200 and 139 (73%) of 191, respectively (appendix).

208 (93%) of 223 patients assigned to trastuzumab emtansine plus pertuzumab and 211 (96%) of 221 assigned to docetaxel, carboplatin, and trastuzumab plus pertuzumab completed all six cycles of neoadjuvant treatment (appendix p 5). Most patients underwent definitive breast cancer surgery within the protocol-specified window of 14 days to 6 weeks after their last dose of neoadjuvant therapy; based on a review of protocol violations by the study team, nine patients in each treatment group had surgery outside the protocol-specified window. In the trastuzumab emtansine plus pertuzumab group, 25 (11%) patients required a reduction in their dose of trastuzumab emtansine.

In the docetaxel, carboplatin, and trastuzumab plus pertuzumab group, 51 patients (23%) required dose reductions of docetaxel and 58 patients (27%) required dose reductions of carboplatin. Dose reductions were most commonly due to adverse events in both groups (in 24 [11%] of 223 patients in the trastuzumab emtansine plus pertuzumab group and in 68 [31%] of 221 in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group).

The most common adverse events leading to dose reductions in the trastuzumab emtansine plus pertuzumab group were laboratory anomalies (21 [9%] of 223), whereas in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group they were gastrointestinal disorders for docetaxel (24 [11%] of 221) and blood and lymphatic system disorders for carboplatin (23 [11%]; information about growth factor use and dose reductions due to adverse events is in the appendix, p 6). In the trastuzumab emtansine plus pertuzumab group, 15 (7%) of 223 patients discontinued at least one component of neoadjuvant treatment because of disease progression and seven (3%) of 223 discontinued at least one component of treatment because of adverse events. In the docetaxel, carboplatin, and trastuzumab plus pertuzumab group, one patient (<1%) of 221 discontinued at least one treatment component because of disease

	Trastuzumab emtansine plus pertuzumab (n=223)		Docetaxel, carboplatin, and trastuzumab plus pertuzumab (n=221)		Proportion of patients achieving a pathological complete response
	Patients, n	Response, n (%)	Patients, n	Response, n (%)	Difference (95% CI)
Age group					
<65 years	198	90 (45·5)	200	115 (57·5)	−12·1 (−21·8 to −2·3)
≥65 years	25	9 (36·0)	21	8 (38·1)	−2·1 (−30·1 to 25·9)
World region					
North America	54	18 (33·3)	54	29 (53·7)	−20·4 (−38·7 to −2·1)
Rest of world	84	42 (50·0)	83	43 (51·8)	−1·8 (−17·0 to 13·4)
Western Europe	85	39 (45·9)	84	51 (60·7)	−14·8 (−29·7 to 0·0)
Clinical stage at diagnosis					
II–IIIA	186	80 (43·0)	183	106 (57·9)	−14·9 (−25·0 to −4·8)
IIIB–IIIC	37	19 (51·4)	38	17 (44·7)	6·6 (−16·0 to 29·2)
Central hormone receptor status					
Oestrogen-receptor and progesterone-receptor-negative	83	45 (54·2)	82	60 (73·2)	−19·0 (−33·3 to −4·6)
Oestrogen-receptor or progesterone-receptor-positive	131	46 (35·1)	128	56 (43·8)	−8·6 (−20·5 to 3·2)
Race					
White	148	65 (43·9)	147	86 (58·5)	−14·6 (−25·9 to −3·3)
Black or African American	5	2 (40·0)	6	3 (50·0)	−10·0 (−68·7 to 48·7)
Asian	60	30 (50·0)	52	27 (51·9)	−1·9 (−20·5 to 16·6)
Other	10	2 (20·0)	16	7 (43·8)	−23·8 (−58·5 to 11·0)
Local hormone receptor status					
Oestrogen-receptor and progesterone-receptor-negative	84	46 (54·8)	83	59 (71·1)	−16·3 (−30·8 to −1·9)
Oestrogen-receptor or progesterone-receptor-positive	139	53 (38·1)	138	64 (46·4)	−8·3 (−19·8 to 3·4)
Baseline ECOG score					
0	209	91 (43·5)	212	117 (55·2)	−11·7 (−21·1 to −2·2)
1	14	8 (57·1)	9	6 (66·7)	−9·5 (−49·8 to 30·7)
All patients	**223**	**99 (44·4)**	**221**	**123 (55·7)**	**−11·3 (−20·5 to −2·0)**

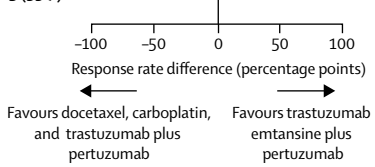

Figure 3: **Subgroup analysis of pathological complete response by baseline factors**
ECOG=Eastern Cooperative Oncology Group. 20 patients had an unknown oestrogen-receptor or progesterone-receptor status by central analysis and are therefore not included in the analysis of pathological complete response by central hormone receptor status.

progression and 17 (8%) of 221 did so because of adverse events. In the trastuzumab emtansine plus pertuzumab group, the adverse events that led to treatment discontinuation in more than one patient were increased alanine aminotransferase (two patients [1%]) and pneumonitis (two [1%]). In the docetaxel, carboplatin, and trastuzumab plus pertuzumab group, adverse events that led to treatment discontinuation in more than one patient were decreased neutrophil count (three patients [1%]), diarrhoea (three [1%]), decreased platelet count (two [1%]), anaemia (two [1%]), febrile neutropenia (two [1%]), and hypersensitivity (two [1%]).

Fewer patients receiving trastuzumab emtansine plus pertuzumab had any adverse events compared with those receiving docetaxel, carboplatin, and trastuzumab plus pertuzumab (197 [88%] of 223 *vs* 216 [99%] of 219; table 2). Patients might have had more than one adverse event. Serious adverse events also occurred less frequently with trastuzumab emtansine plus pertuzumab (11 [5%] of 223 *vs* 63 [29%] of 219), and no single serious adverse event occurred in 1% or more of patients treated with trastuzumab emtansine plus pertuzumab, whereas the following serious adverse events occurred in at least 1% of treated patients in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group: febrile neutropenia (26 [12%] of 219), neutropenia (seven [3%]), diarrhoea (nine [4%]), vomiting (four [2%]), colitis (three [1%]), and decreased neutrophil count (three [1%]).

Fewer patients in the trastuzumab emtansine plus pertuzumab group had a grade 3–4 adverse event than in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group (29 [13%] of 223 *vs* 141 [64%] of 219;

table 2). The most frequently occurring grade 3–4 adverse events with trastuzumab emtansine plus pertuzumab were decreased platelet count, fatigue, increased alanine aminotransferase, and hypokalaemia (table 2). The most common grade 3–4 adverse events with docetaxel, carboplatin, and trastuzumab plus pertuzumab were neutropenia, diarrhoea, and febrile neutropenia (table 2). One (<1%) of 223 patients in the trastuzumab emtansine plus pertuzumab group (grade 2 severity) and none in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group had a CTCAE ejection fraction decrease. No deaths occurred during neoadjuvant treatment. Chronic cardiac failure of grade 1 occurred in no patients in the trastuzumab emtansine plus pertuzumab group and in one patient (<1%) of 219 in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group.

Discussion

The results of this trial show that significantly more patients receiving neoadjuvant docetaxel, carboplatin, and trastuzumab plus pertuzumab achieved a pathological complete response than those receiving trastuzumab emtansine plus pertuzumab, as determined by study-trained local pathologists.[21] Consistent with this finding, neoadjuvant docetaxel, carboplatin, and trastuzumab plus pertuzumab was also associated with more patients receiving breast-conserving surgery and fewer discontinuing treatment because of disease progression. However, neoadjuvant trastuzumab emtansine plus pertuzumab was associated with fewer grade 3–4 adverse events than systemic chemotherapy-based treatment. As expected, the incidence of adverse events associated with docetaxel and carboplatin, such as bone marrow toxicity, were lower with the trastuzumab emtansine plus pertuzumab regimen (which did not include these drugs). Decreases in LVEF were rare in both groups compared with doxetaxel, carboplatin, and trastuzumab plus pertuzumab. Compared with docetaxel, carboplatin, and trastuzumab plus pertuzumab, trastuzumab emtansine plus pertuzumab was associated with numerically longer maintenance of patient-reported HRQOL (median time to deterioration of 4·63 months with trastuzumab emtansine *vs* 3·02 months with docetaxel, carboplatin, and trastuzumab plus pertuzumab) and physical function (median time to deterioration of 4·86 months *vs* 2·79 months); however, HRQOL scores were poor in both groups at the end of therapy (appendix, p 10). Collectively, these results support the neoadjuvant systemic chemotherapy regimen of docetaxel, carboplatin, and trastuzumab plus pertuzumab remaining as the standard of care, although less intensive therapeutic options, including therapy based on trastuzumab emtansine plus pertuzumab or the adjuvant paclitaxel and trastuzumab regimen,[22] might be a suitable treatment option for patients unlikely to tolerate systemic taxane-based chemotherapy.

	Trastuzumab emtansine plus pertuzumab (n=223)			Docetaxel, carboplatin, and trastuzumab plus pertuzumab (n=219)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Nausea	76 (34%)	0	0	125 (57%)	3 (1%)	0
Diarrhoea	72 (32%)	2 (<1%)	0	128 (58%)	32 (15%)	1 (<1%)
Fatigue	62 (28%)	3 (1%)	0	81 (37%)	7 (3%)	0
Headache	51 (23%)	1 (<1%)	0	27 (12%)	1 (<1%)	0
Alanine aminotransferase increased	45 (20%)	3 (1%)	0	18 (8%)	4 (2%)	0
Aspartate aminotransferase increased	32 (14%)	1 (<1%)	0	16 (7%)	1 (<1%)	0
Asthenia	31 (14%)	0	0	49 (22%)	6 (3%)	0
Rash	30 (14%)	0	0	48 (22%)	1 (<1%)	0
Epistaxis	29 (13%)	1 (<1%)	0	23 (11%)	0	0
Dysgeusia	22 (10%)	0	0	43 (20%)	0	0
Pyrexia	22 (10%)	0	0	26 (12%)	2 (<1%)	0
Vomiting	17 (8%)	1 (<1%)	0	61 (28%)	7 (3%)	0
Constipation	15 (7%)	0	0	37 (17%)	0	0
Dizziness	15 (7%)	0	0	18 (8%)	1 (<1%)	0
Decreased appetite	14 (6%)	0	0	32 (15%)	3 (1%)	0
Stomatitis	14 (6%)	0	0	47 (22%)	1 (<1%)	0
Abdominal pain	13 (6%)	1 (<1%)	0	26 (12%)	2 (<1%)	0
Anaemia	13 (6%)	2 (<1%)	0	54 (25%)	21 (10%)	0
Mucosal inflammation	10 (5%)	0	0	28 (13%)	1 (<1%)	0
Hypertension	8 (4%)	1 (<1%)	0	7 (3%)	7 (3%)	0
Peripheral sensory neuropathy	8 (4%)	1 (<1%)	0	18 (8%)	0	0
Upper respiratory tract infection	8 (4%)	0	0	7 (3%)	1 (<1%)	0
Anxiety	7 (3%)	0	0	9 (4%)	1 (<1%)	0
Neuropathy peripheral	7 (3%)	0	1 (<1%)	20 (9%)	1 (<1%)	0
Thrombocytopenia	7 (3%)	0	1 (<1%)	18 (8%)	3 (1%)	1 (<1%)
Weight decreased	7 (3%)	0	0	18 (8%)	1 (<1%)	0
Back pain	6 (3%)	1 (<1%)	0	12 (6%)	0	0
Platelet count decreased	6 (3%)	2 (<1%)	1 (<1%)	16 (7%)	9 (4%)	2 (<1%)
Alopecia	4 (2%)	0	0	138 (63%)	2 (<1%)	0
Hypokalaemia	4 (2%)	3 (1%)	0	12 (6%)	5 (2%)	0
Pain	4 (2%)	0	0	9 (4%)	1 (<1%)	0
Abdominal pain upper	3 (1%)	0	0	15 (7%)	1 (<1%)	0
Hypersensitivity	3 (1%)	0	0	7 (3%)	1 (<1%)	0
Dehydration	2 (<1%)	0	0	8 (4%)	3 (1%)	0
Device-related infection	2 (<1%)	0	0	1 (<1%)	1 (<1%)	0
Gastritis	2 (<1%)	1 (<1%)	0	3 (1%)	0	0
Gastroenteritis	2 (<1%)	1 (<1%)	0	0	1 (<1%)	0
Syncope	2 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0
Dysuria	1 (<1%)	0	0	7 (3%)	1 (<1%)	0
Leucopenia	1 (<1%)	0	0	7 (3%)	2 (<1%)	1 (<1%)
Neutrophil count decreased	1 (<1%)	0	0	3 (1%)	6 (3%)	14 (6%)
Pneumonia	1 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0
Pneumonitis	1 (<1%)	1 (<1%)	0	0	0	0
Deep vein thrombosis	0	1 (<1%)	0	0	0	0
γ-glutamyltransferase increased	0	1 (<1%)	0	2 (<1%)	0	0
Hypertensive crisis	0	1 (<1%)	0	0	0	0
Hypoalbuminaemia	0	1 (<1%)	0	1 (<1%)	0	0
Neutropenia	0	1 (<1%)	0	7 (3%)	20 (9%)	35 (16%)

(Table 2 continues on next page)

	Trastuzumab emtansine plus pertuzumab (n=223)			Docetaxel, carboplatin, and trastuzumab plus pertuzumab (n=219)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Wound infection	0	1 (<1%)	0	0	0	0
Acute kidney injury	0	0	1 (<1%)	1 (<1%)	1 (<1%)	0
Bacteraemia	0	0	1 (<1%)	0	0	0
Respiratory failure	0	0	1 (<1%)	0	0	0
Hypomagnesaemia	0	0	0	9 (4%)	1 (<1%)	0
White blood cell count decreased	0	0	0	6 (3%)	9 (4%)	0
Dysaesthesia	0	0	0	2 (<1%)	1 (<1%)	0
Sinus tachycardia	0	0	0	2 (<1%)	1 (<1%)	0
Vaginal inflammation	0	0	0	2 (<1%)	1 (<1%)	0
Rash erythematous	0	0	0	1 (<1%)	1 (<1%)	0
Subcutaneous abscess	0	0	0	1 (<1%)	1 (<1%)	0
Febrile neutropenia	0	0	0	0	23 (11%)	10 (5%)
Colitis	0	0	0	0	4 (2%)	0
Adenomyosis	0	0	0	0	1 (<1%)	0
Clostridium difficile infection	0	0	0	0	1 (<1%)	0
Diarrhoea infectious	0	0	0	0	1 (<1%)	0
Gastrointestinal haemorrhage	0	0	0	0	1 (<1%)	0
Gastroenteritis norovirus	0	0	0	0	1 (<1%)	0
Hypermagnesaemia	0	0	0	0	1 (<1%)	0
Kidney infection	0	0	0	0	1 (<1%)	0
Osteoarthritis	0	0	0	0	1 (<1%)	0
Pulmonary embolism	0	0	0	0	1 (<1%)	0
Small intestinal obstruction	0	0	0	0	1 (<1%)	0
Procedural intestinal perforation	0	0	0	0	1 (<1%)	0
Subcutaneous haematoma	0	0	0	0	1 (<1%)	0
Sepsis	0	0	0	0	0	2 (<1%)
Anaphylactic reaction	0	0	0	0	0	1 (<1%)
Enterocolitis infectious	0	0	0	0	0	1 (<1%)

Data are all grade 1 or grade 2 adverse events (n [%]) that occurred in ≥10% of patients in either treatment group and all grade 3 and grade 4 adverse events. No deaths occurred in either group. Patients might have had more than one adverse event.

Table 2: **Adverse events**

The proportion of patients achieving a pathological complete response with trastuzumab emtansine plus pertuzumab is similar to neoadjuvant data from the phase 2 West German Study Group Adjuvant Dynamic marker Adjusted Personalized Therapy (WSG-ADAPT) study,[23] which showed that more than 40% of patients with HER2-positive or hormone receptor-positive early-stage breast cancer treated with this regimen achieved a pathological complete response. In our study, our subgroup analysis showed that a high percentage of patients with hormone receptor-negative disease achieved a pathological complete response, irrespective of which therapeutic regimen they received. A similar result was recorded in the TRYPHAENA study,[24] which assessed the cardiac safety of pertuzumab and trastuzumab plus standard neoadjuvant chemotherapy in patients with HER2-positive early breast cancer. In TRYPHAENA, the proportion of patients achieving a pathological complete response (defined as *y*pT0/is) was assessed in three treatment groups (chemotherapy, trastuzumab, and pertuzumab; chemotherapy followed by docetaxel, trastuzumab, and pertuzumab; and docetaxel, carboplatin, and trastuzumab plus pertuzumab), and was higher in patients with hormone receptor-negative disease (achieved in 84% of patients with docetaxel, carboplatin, and trastuzumab plus pertuzumab) than in those with hormone receptor-positive disease in all three treatment groups (achieved in 50% with docetaxel, carboplatin, and trastuzumab plus pertuzumab). Results from TRYPHAENA and our study suggest that patients with hormone receptor-negative HER2-positive breast cancer are more likely to achieve a pathological complete response with standard chemotherapy plus HER2-targeted therapy than do patients with hormone receptor-negative disease, and therefore de-escalation of the chemotherapy regimen (eg, to trastuzumab emtansine or a chemotherapy-free regimen) might not be the best option for these patients. By contrast, de-escalation of standard chemotherapy might be more appropriate in patients with hormone receptor-positive disease, such as in the WSG-ADAPT study.[23]

The phase 3 MARIANNE study[25] showed non-inferior efficacy and better tolerability of first-line trastuzumab emtansine and trastuzumab emtansine plus pertuzumab versus systemic chemotherapy for HER2-positive metastatic breast cancer. The MARIANNE results, together with data from WSG-ADAPT, suggest that trastuzumab emtansine alone is sufficient without pertuzumab. These findings might provide the rationale for further research into predictive biomarkers, to better assess which patients are most likely to benefit, as well as the investigation of other neoadjuvant regimens that omit traditional systemic chemotherapy. Prespecified biomarker analyses of samples from our study participants are ongoing, including an assessment of the cancer-burden index in each treatment group and any correlation with survival outcomes.

Strengths of this study included its prospective design and aim to study a novel therapeutic regimen without traditional chemotherapy. Investigating a treatment regimen without traditional chemotherapy is valuable in this patient population where quality of life and side-effect profiles are important. This study was limited by the use of pathological complete response as a primary outcome, the absence of central pathology review, the absence of a trastuzumab emtansine monotherapy group, and the absence of a response-guided approach to chemotherapy. Pathological complete response has been shown to correlate with with long-term outcomes in many studies.[26] This is a good surrogate endpoint for longer-term outcomes because studies that use pathological complete response as their primary outcome require fewer patients and the outcome is assessed at a shorter follow-up time. Thus, this option is more ethical and affordable. However, pathological

complete response is still a surrogate for longer-term outcomes. We are following event-free survival, invasive disease-free survival, and overall survival, and these findings will be reported in the future. The association between the absence of pathological complete response and disease-free survival or overall survival in the oestrogen-receptor-positive, HER2-positive patient subgroup is uncertain given that endocrine therapy is used after surgery in this subset of patients. Because pathology was not centrally reviewed, information about the proportions of HER2 positivity and HER2 negativity in the residual tumour is not available. Such information might be useful in further understanding the differences in pathological complete response between treatment groups and the effect of chemotherapy targeting only HER2-positive cells in the trastuzumab emtansine plus pertuzumab group. Additionally, a trastuzumab emtansine monotherapy group would have provided a comparator that would allow us to fully assess the effect of pertuzumab combined with trastuzumab emtansine. Furthermore, although response-guided chemotherapy was not part of this trial design, studies using such an approach would be useful to investigate whether or not traditional chemotherapy can be omitted in patients with a pathological complete response. Additional insights into the use of trastuzumab emtansine in the treatment of HER2-positive early-stage breast cancer, including the effect on long-term outcomes such as disease-free survival and overall survival, will be provided by two ongoing phase 3 trials in the adjuvant setting: KATHERINE (NCT01772472; trastuzumab emtansine *vs* trastuzumab in patients without a pathological complete response); and KAITLIN (NCT01966471; trastuzumab emtansine plus pertuzumab *vs* trastuzumab and pertuzumab plus taxane following anthracycline-based chemotherapy); and the phase 2 ATEMPT study (NCT01853748; trastuzumab emtansine *vs* trastuzumab and paclitaxel in patients with stage I HER2-positive breast cancer).

To our knowledge, the KRISTINE study is the first phase 3 trial in patients with HER2-positive breast cancer to assess whether traditional systemic chemotherapy can be omitted in the neoadjuvant setting. In the neoadjuvant setting, where the ultimate aim of treatment is to prevent disease recurrence, the use of HER2 blockade plus traditional chemotherapy remains the standard therapeutic approach to optimising the number of patients achieving a pathological complete response, but future efforts should improve the efficacy of chemotherapy without imparting more toxicity. Results from the adjuvant phase of KRISTINE will be reported in the future.

Contributors

SAH contributed to study design, data collection and interpretation, and manuscript writing and revision. MM, KHJ, C-SH, VV, DSt, HW, JS, and DSl contributed to study design, data collection and interpretation, and manuscript revision. WFS, AMT, and NH contributed to study design, data interpretation, and manuscript revision. MC, J-FB, and MWB contributed to data collection and interpretation and manuscript revision. KA and RF contributed to study design; development of the case report forms and study database; data analysis, validation, cleaning, and interpretation, and manuscript revision. H-JH, JX, and YGL contributed to study design, data analysis and interpretation, and manuscript writing and revision.

Declaration of interests

SAH has received honoraria from F Hoffmann-La Roche, Genentech and travel support from F Hoffmann-La Roche, Boehringer Ingelheim, Novartis, Lilly, Pfizer, and Bayer. Her institution has received research funding from F Hoffmann-La Roche, Genentech, Novartis, GlaxoSmithKline, Boehringer Ingelheim, Sanofi, Pfizer, Amgen, OBI Pharma, Puma Biotechnology, Dignitana, Bayer, BioMarin, Lilly, and Merrimack. MM has served as a consultant for F Hoffmann-La Roche, Genentech, Novartis, and AstraZeneca. His institution has received research funding from Novartis and from Centro de Investigación Biomédica en Red in the thematic area of Breast Oncology (CIBERONC Breast), of the Instituto de Salud Carlos III (ISCIII). WFS owns stock in IONIS Pharmaceuticals and Nuvera Biosciences, has received honoraria from Affymetrix, owns intellectual property in Nuvera Biosciences, and has received travel support from AbbVie. C-SH has received honoraria from F Hoffmann-La Roche and Novartis, received travel support from F Hoffmann-La Roche and Amgen, and has served as a consultant for F Hoffmann-La Roche. His institution has received research funding from F Hoffmann-La Roche, Genentech, Amgen, Novartis, OBI Pharma, Boehringer Ingelheim, BioMarin, AstraZeneca, Lilly, Pfizer, and AbbVie. NH has received honoraria from F Hoffmann-La Roche, Genentech and Novartis. VV has received research funding and consulting honoraria from F Hoffmann-La Roche and Genentech, and travel support from F Hoffmann-La Roche. HW has served as a consultant for, and received research funding and travel support from, F Hoffman-La Roche. MC has served as a consultant for Pfizer, Astra Zeneca, and Lilly; and has received grant support and personal fees from Novartis. J-FB has received honoraria from F Hoffmann-La Roche, Novartis, Pfizer, and Amgen, has served as a consultant for F Hoffmann-La Roche, has received travel support from F Hoffmann-La Roche, GlaxoSmithKline, and Novartis, and has received research funding from F Hoffmann-La Roche, Pfizer, and AbbVie. KA has received travel support from F Hoffmann-La Roche. RF has received travel support from F Hoffmann-La Roche and Genentech. H-JH is a salaried employee of, and owns stock in, F Hoffmann-La Roche. JX and YGL are salaried employees of Genentech and own stock in F Hoffmann-La Roche. JS owns stock in Metastat and has served as a consultant for F Hoffmann-La Roche, Genentech, Eisai, Novartis, Johnson & Johnson, Curis, Sanofi, AstraZeneca, and Celgene. His institution has received research funding from Merck. DSl owns stock in Pfizer and Amgen, has received consulting fees from Novartis and Pfizer, and research funding from Bayer and Novartis. KHJ, AMT, MWB, and DSt declare no competing interests.

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