Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study

Josep Tabernero, Paulo M Hoff, Lin Shen, Atsushi Ohtsu, Manish A Shah, Karen Cheng, Chunyan Song, Haiyan Wu, Jennifer Eng-Wong, Katherine Kim, Yoon-Koo Kang

Lancet Oncol 2018; 19: 1372–84

Published Online
September 11, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30481-9

See Comment page 1270

Vall d'Hebron University Hospital and Institute of Oncology, Universitat Autonoma de Barcelona, Centro de Investigación Biomédica en Red Cáncer, Barcelona, Spain (J Tabernero MD); **Instituto do Cancer de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil** (P M Hoff MD); **Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Gastrointestinal Oncology, Peking University Cancer Hospital and Institute, Beijing, China** (Prof L Shen MD); **Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan** (A Ohtsu MD); **Meyer Cancer Center at Weill Cornell Medical College, Medical Oncology/Solid Tumor Program, New York, NY, USA** (M A Shah MD); **Product Development Oncology, Genentech Inc, South San Francisco, CA, USA** (K Cheng PharmD, C Song MD, J Eng-Wong MD, K Kim MPH); **Biostatistics, Biometrics, Roche Holding Ltd, Shanghai, China** (H Wu PhD); **and Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea** (Prof Y-K Kang MD)

Correspondence to:
Prof Yoon-Koo Kang, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 05505 South Korea
ykkang@amc.seoul.kr

Summary

Background Adding pertuzumab to trastuzumab and chemotherapy improves survival in HER2-positive early breast cancer and metastatic breast cancer. We assessed the efficacy and safety of pertuzumab versus placebo in combination with trastuzumab and chemotherapy in first-line HER2-positive metastatic gastric or gastro-oesophageal junction cancer.

Methods JACOB was a double-blind, placebo-controlled, randomised, multicentre, phase 3 trial in patients aged 18 years or older with HER2-positive metastatic gastric or gastro-oesophageal junction cancer. Eligible patients had measurable or evaluable non-measurable disease at baseline, Eastern Cooperative Oncology Group performance status of 0 or 1, and baseline left ventricular ejection fraction of 55% or more. Patients at 197 oncology clinics (in 30 countries) were randomly assigned (1:1) to receive either pertuzumab (840 mg intravenously) or placebo every 3 weeks, with trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks intravenously), plus chemotherapy (cisplatin 80 mg/m² every 3 weeks intravenously, oral capecitabine 1000 mg/m² twice a day [2000 mg/m² every 24 h] for 28 doses every 3 weeks, or 5-fluorouracil 800 mg/m² every 24 h intravenously [120 h continuous infusion] every 3 weeks). Randomisation was by a central permuted block randomisation scheme (block size of 4) with an interactive voice or web response system, stratified by geographical region, previous gastrectomy, and HER2 positivity. The primary endpoint was overall survival in the intention-to-treat population. This trial is registered with Clinicaltrials.gov, number NCT01774786 (ongoing, but closed to enrolment).

Findings Between June 10, 2013, and Jan 12, 2016, of 3287 patients assessed, 780 eligible patients were randomly assigned to receive either pertuzumab plus trastuzumab and chemotherapy (pertuzumab group, n=388) or placebo plus trastuzumab and chemotherapy (control group, n=392). Median duration of follow-up was 24·4 months (95% CI 22·3–26·1) in the pertuzumab group and 25·0 months (22·3–28·9) in the control group. After 242 deaths in the pertuzumab group and 262 deaths in the control group (the study was not stopped at this point), overall survival was not significantly different between treatment groups (median overall survival 17·5 months [95% CI 16·2–19·3] in the pertuzumab group and 14·2 months [12·9–15·5] in the control group; hazard ratio 0·84 [95% CI 0·71–1·00]; p=0·057). Serious adverse events occurred in 175 (45%) of 385 patients in the pertuzumab group and 152 (39%) of 388 patients in the control group. Diarrhoea was the most common serious adverse event in both groups (17 [4%] patients in the pertuzumab group *vs* 20 [5%] patients in the control group). The most common grade 3–5 adverse events were neutropenia (116 [30%] patients in the pertuzumab group *vs* 108 [28%] patients in the control group), anaemia (56 [15%] *vs* 65 [17%]), and diarrhoea (51 [13%] *vs* 25 [6%]). Treatment-related deaths occurred in seven (2%) patients in the control group; no treatment-related deaths occurred in the pertuzumab group.

Interpretation Adding pertuzumab to trastuzumab and chemotherapy did not significantly improve overall survival in patients with HER2-positive metastatic gastric or gastro-oesophageal junction cancer compared with placebo. Further studies are needed to identify improved first-line treatment options in these types of cancer and to identify patients with HER2-driven tumours who might benefit from dual HER2-targeted therapy.

Funding F. Hoffmann-La Roche Ltd.

Introduction

Globally, stomach (gastric) cancer is the fifth most common cancer (after lung, breast, colorectal, and prostate cancer) and the third most common cause of cancer-related death.[1] Worldwide, an estimated 925 000 new cases of stomach cancer were diagnosed in 2012, accounting for approximately 8·8% of global cancer deaths that year.[1]

Targeted treatments that have substantial efficacy and acceptable toxicity have long been needed in gastric cancer. HER2 overexpression or amplification has been

Research in context

Evidence before this study

During the development and finalisation of the JACOB study protocol, we reviewed the scientific literature to assess current treatment and unmet needs of patients with advanced gastric cancer. We searched PubMed and congress abstracts published by the American Society of Clinical Oncology Annual Meeting, the Gastrointestinal Cancers Symposium, and the European Society for Medical Oncology for potentially relevant publications using the terms "gastric cancer", "HER2", "HER2 overexpression", "trastuzumab", "pertuzumab", and "HER2-positive breast cancer" excluding non-English publications. Relevant articles published up to Aug 30, 2012, were selected for further review. The literature searches confirmed that although trastuzumab plus a combined fluoropyrimidine or platinum-based drug chemotherapy regimen is the global standard of care in patients with HER2-positive metastatic gastric cancer, there remains an unmet clinical need for effective therapies in this disease. Evidence from reports of non-clinical studies in gastric cancer models and clinical studies in metastatic breast cancer suggested that pertuzumab might augment the antitumour effects of trastuzumab against HER2-positive tumours, with or without chemotherapy. Available clinical trial data also suggested that the addition of pertuzumab to trastuzumab and chemotherapy led to improved efficacy, with an acceptable safety profile.

Added value of this study

We report the primary analysis of a double-blind, randomised, phase 3 trial investigating the efficacy and safety of the addition of pertuzumab to trastuzumab and chemotherapy as a first-line treatment for patients with advanced HER2-positive metastatic gastric or gastro-oesophageal junction cancer. Our trial, JACOB, did not meet its primary endpoint of showing a significant improvement in overall survival in patients who received pertuzumab compared with those who did not. Notably, the addition of pertuzumab to trastuzumab plus chemotherapy and administration of 840 mg pertuzumab every 3 weeks, instead of the 420 mg every 3 weeks currently approved for maintenance regimens in breast cancer, did not lead to increased rates of adverse cardiac events or to the emergence of any new safety signals, and did not have a clinically meaningful effect on health-related quality of life. This study adds to evidence suggesting that the tumour biology of HER2-positive advanced gastric cancer is intrinsically different from that of HER2-positive breast cancer, including potential differences in the role of HER2 in driving disease progression and therapeutic responses to targeted therapies.

Implications of all the available evidence

The results from the JACOB trial suggest that adding pertuzumab to trastuzumab and chemotherapy for first-line treatment of HER2-positive metastatic gastric or gastro-oesophageal junction cancer does not significantly improve overall survival compared with the current standard of care. Further research is required to identify first-line treatment options to improve outcomes in this patient population. Further exploration of the tumour biology and the key drivers of disease progression in HER2-positive gastric cancers might help to better identify patients with HER2-driven tumours who could benefit from dual HER2-targeted regimens.

identified as a potential prognostic factor and is considered a valid therapeutic target.[2–4] In the Trastuzumab for Gastric Cancer (ToGA) trial,[5] the addition of the HER2-targeted monoclonal antibody trastuzumab to cisplatin or fluoropyrimidine doublet chemotherapy (capecitabine plus cisplatin or fluorouracil plus cisplatin) significantly improved overall survival in patients with previously untreated HER2-positive locally advanced or metastatic gastric cancer or gastro-oesophageal junction cancer compared with chemotherapy alone. A post-hoc analysis of the ToGA trial noted that trastuzumab showed increased efficacy in patients with higher levels of HER2 overexpression—ie, those with tumours that were immunohistochemistry (IHC) 3+ regardless of fluorescence in-situ hybridisation (FISH) status, or were IHC 2+ and FISH positive—compared with patients with lower levels of HER2 expression (IHC 1+ and FISH positive or IHC 0+ and FISH positive). Trastuzumab plus chemotherapy with capecitabine or fluorouracil plus a platinum-based drug, such as cisplatin, is now the first-line standard of care treatment in patients with HER2-positive metastatic gastric cancer.[6,7]

Pertuzumab, a humanised monoclonal HER2-targeted antibody that binds to a different epitope on the HER2 receptor protein than trastuzumab, has been shown to significantly improve survival outcomes when added to trastuzumab plus chemotherapy in patients with HER2-positive early and metastatic breast cancer.[8–10] Although the biology of HER2-positive gastric cancer or gastro-oesophageal junction cancer might differ from that of HER2-positive breast cancer—including differences in HER2 expression patterns (eg, HER2 heterogeneity is more common in gastric cancer)[11]—the addition of pertuzumab to trastuzumab and chemotherapy is hypothesised to further improve overall survival in patients with HER2-positive advanced gastric cancer or gastro-oesophageal junction cancer, especially in those with high levels of HER2 overexpression, who derived more benefit from the addition of trastuzumab to standard chemotherapy in the ToGA trial.[5] Until now, this hypothesis has not been tested in a phase 3 trial.

The pharmacokinetics and safety of pertuzumab plus trastuzumab and chemotherapy in patients with advanced gastric cancer were assessed in the phase 2a JOSHUA trial.[12] This study showed that a treatment regimen of 840 mg pertuzumab every 3 weeks produced higher serum trough concentrations than an 840 mg loading dose followed by a 420 mg maintenance dose,

resulting in trough concentrations in patients with HER2-positive advanced gastric cancer that were similar to those seen in patients with HER2-positive metastatic breast cancer, while maintaining a similar adverse event profile to the 840 mg followed by 420 mg regimen.[12,13] On the basis of these findings, we selected an 840 mg dose of pertuzumab every 3 weeks (loading plus maintenance) for investigation in the phase 3 JACOB study (NCT01774786). We compared the efficacy and safety of pertuzumab in addition to trastuzumab and chemotherapy versus placebo plus trastuzumab and chemotherapy as first-line therapy in patients with previously untreated HER2-positive metastatic gastric cancer or gastro-oesophageal junction cancer.

See Online for appendix

Methods

Study design and participants

The JACOB study was a double-blind, placebo-controlled, randomised phase 3 trial done in 197 oncology clinics across 30 countries (appendix pp 2–8). Patients were aged 18 years or older and had HER2-positive, histologically confirmed metastatic adenocarcinoma of the stomach or gastro-oesophageal junction cancer. We defined HER2 positivity as IHC 3+ or IHC 2+ and in-situ hybridisation (ISH)-positive, determined by testing at a central laboratory (Targos Molecular Pathology GmbH, Kassel, Germany [or for the Chinese sites only, Q-Lab, Shanghai, China]) using PATHWAY anti-HER2/neu (4B5) IHC (Ventana Medical Systems, Tucson, AZ, USA) and the INFORM HER2 Dual ISH assay (Ventana Medical Systems, Tucson, AZ, USA). We did testing on either primary or metastatic tumour tissue, which was supplied as one of a formalin-fixed paraffin-embedded tissue block, a partial block, or freshly cut unstained slides. Patients were required to have measurable disease or evaluable non-measurable disease at baseline according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria, Eastern Cooperative Oncology Group performance status 0 or 1, baseline left ventricular ejection fraction (LVEF) of 55% or more, and a life expectancy of at least 3 months. Clinical laboratory tests were performed within 7 days before the first dose of study treatment and patients were required to have an absolute neutrophil count of at least 1500 cells per µL, platelet count of at least 75 000 per µL, haemoglobin concentration of at least 9·0 g/dL, creatinine clearance of at least 60 mL/min per 1·73 m² (Cockcroft-Gault formula), total serum bilirubin concentration of up to 1·5×upper limit of normal (ULN) of laboratory range, adequate hepatic function (in patients with no liver and no bone metastases: aspartate aminotransferase [AST] concentration or alanine aminotransferase [ALT] concentration of ≤1·5×ULN and alkaline phosphatase [ALP] concentration of ≤2·5×ULN, or AST or ALT concentration of ≤2·5×ULN; in patients with liver metastases but no bone metastases: AST or ALT of ≤5×ULN and ALP of ≤2·5×ULN; in patients with liver and bone metastases: AST or ALT ≤5×ULN and ALP ≤10×ULN; in patients with bone metastases but no liver metastases: AST or ALT ≤1·5×ULN and ALP ≤10×ULN), serum albumin concentration of at least 25 g/L, and a negative serum pregnancy test (in patients of childbearing potential). We excluded patients with documented history of congestive heart failure, angina pectoris requiring treatment, myocardial infarction within 6 months before the first study dose of study treatment, clinically significant valvular heart disease or uncontrollable high-risk cardiac arrhythmia, or history or evidence of poorly controlled hypertension. Patients who had received previous therapy with a HER2-targeted drug or previous systemic cytotoxic chemotherapy for metastatic disease were also excluded. Full inclusion and exclusion criteria are listed in the appendix (pp 9–10). Patients were required to provide written informed consent.

JACOB was done in accordance with the International Conference on Harmonisation E6 guideline for Good Clinical Practice (ICH–GCP E6) and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was done, whichever provided the greater protection for the individual. The protocol was amended once for clarity and consistency around protocol procedures, assessments, and analyses (amendment date March 4, 2014; amendment approved by relevant institutional review board or ethics committee and regulatory authorities as required). The amendments did not result in substantial changes to the study objectives, patient eligibility criteria, or safety and efficacy assessments and analyses. The study protocol is available in the appendix.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive pertuzumab plus trastuzumab and chemotherapy (pertuzumab group) or placebo plus trastuzumab and chemotherapy (control group). We performed central randomisation and drug pack number allocation using a permuted block randomisation scheme (block size of 4) with an interactive voice or web response system (IxRS). We gave a patient number and treatment assignment to the investigator via IxRS at enrolment (the investigator was masked to treatment allocation). Stratification factors were geographical region (Japan *vs* North America or western Europe or Australia *vs* Asia [excluding Japan] *vs* South America or eastern Europe), previous gastrectomy (yes *vs* no), and HER2 positivity (IHC 3+ *vs* IHC 2+ and ISH-positive). Staff at the study site, study monitors, project statisticians, and project team members were masked to treatment allocation. The pertuzumab-matching placebo had an identical formulation and appearance to the pertuzumab treatment but did not contain the antibody. Pertuzumab or placebo was labelled according to the regulatory requirements of each country in which this study was done, and in accordance with ICH–GCP E6.

Procedures

The pertuzumab group received pertuzumab 840 mg every 3 weeks intravenously, with trastuzumab (8 mg/kg loading dose [day 1] intravenously, followed by 6 mg/kg every 3 weeks) plus chemotherapy (cisplatin 80 mg/m² every 3 weeks intravenously, capecitabine 1000 mg/m² taken orally twice a day [2000 mg/m² every 24 h] for 28 doses every 3 weeks, or 5-fluorouracil 800 mg/m² every 24 h intravenously by continuous infusion for 120 h every 3 weeks; appendix p 11). The control group received pertuzumab-matched placebo plus trastuzumab and chemotherapy according to the same regimen as the pertuzumab group. At or before cycle 6, chemotherapy was discontinued only for progressive disease or unacceptable toxicity. Continuation of chemotherapy after cycle 6 was at the discretion of the patient and treating physician. After completion or discontinuation of chemotherapy treatment, all patients continued to receive pertuzumab plus trastuzumab or placebo plus trastuzumab until disease progression, unacceptable toxicity, or withdrawal from the study for another reason. No dose reduction was permitted for pertuzumab or placebo. No dose reduction was permitted for trastuzumab, with the exception of changes of more than 10% in bodyweight, which required recalculation of the dose. Chemotherapy doses were not modified for any bodyweight change of less than 10% but dose reduction and dose delays were permitted for toxicities attributed to cisplatin, capecitabine, or 5-fluorouracil. Pertuzumab or placebo plus trastuzumab administration could be delayed to assess or treat adverse events. If a patient missed a dose of pertuzumab or placebo for any cycle and the time between doses was 6 weeks or more, the standard 840 mg dose of pertuzumab or placebo was given. If pertuzumab or placebo or trastuzumab was held for more than two cycles, or needed to be permanently discontinued, the patient was withdrawn from the study. Patients could receive other anticancer therapies after stopping study treatment at the discretion of the treating physician.

Tumour assessments with CT or MRI scans of the chest, abdomen, and pelvis were done every 9 weeks (or within 7 days before or after this point) until patient death or disease progression.

Incidence and severity of adverse events and serious adverse events were monitored by investigators throughout the study period. The Independent Data Monitoring Committee assessed safety on an ongoing basis. Patients with potentially symptomatic left ventricular systolic dysfunction (LVSD) per investigator assessment were also reviewed by an independent Cardiac Review Committee. LVEF was assessed by echocardiography, multiple-gated acquisition, or cardiac MRI at baseline, and during the study at least every 9 weeks during chemotherapy treatment and every 12 weeks during antibody treatment.

Patient-reported outcome questionnaires were completed at baseline (day 1 of cycle 1), on day 1 of each cycle, at the end of treatment, and at follow-up visits after treatment. Patient-reported outcome questionnaires were completed before all other assessments at each cycle.

Blood samples were taken for pharmacokinetic analyses (data presented elsewhere).[14] Laboratory assessments for haematology and biochemistry analyses were done before dosing in each treatment cycle, at post-treatment monitoring visit 1, and at patient withdrawal from study treatment.

Outcomes

The primary endpoint was overall survival, defined as the time from the date of randomisation to the date of death from any cause. Secondary efficacy endpoints were progression-free survival (defined as the time between the day of randomisation and the date of first documentation of progressive disease assessed by an investigator [per RECIST criteria] or death, whichever occurred first), the proportion of patients who achieved an overall objective response (defined as either a confirmed complete or partial objective response as determined by the RECIST criteria based on an investigator assessment confirmed by a repeat assessment done no less than 4 weeks later), duration of objective response (the time between the date of first documented objective response and the date of first documented progressive disease or death, whichever occurred first), and the proportion of patients who achieved a clinical benefit (defined as a best response of complete or partial objective response or stable disease for 6 weeks or longer, assessed by an investigator).

Safety endpoints included incidence of symptomatic LVSD (defined as an absolute decrease from baseline of ≥10 percentage points in LVEF to a value <50% plus at least one symptom of probable cardiac failure), incidence of asymptomatic LVSD (defined as an absolute decrease from baseline of ≥10 percentage points in LVEF to a value <50%, or asymptomatic decrease in LVEF that required treatment or led to discontinuation of pertuzumab and trastuzumab or placebo and trastuzumab).

Health-related quality of life (HRQoL), time-to-deterioration (TTD) in gastric cancer disease-related symptoms, and treatment-related symptoms were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (v3·0), and the EORTC QLQ-STO22, and EQ-5D-3L questionnaires. EQ-5D outcomes were used for economic modelling purposes and are not reported here. TTD was assessed as TTD1 (time from baseline to the first instance of the patient's score showing a ≥10-point increase in four prespecified symptom scales: abdominal pain, eating restrictions, appetite loss, and fatigue) and TTD2 (TTD from starting trastuzumab and pertuzumab or placebo therapy—ie, TTD from an assessment when a patient had stopped chemotherapy and started treatment with biological therapy alone).

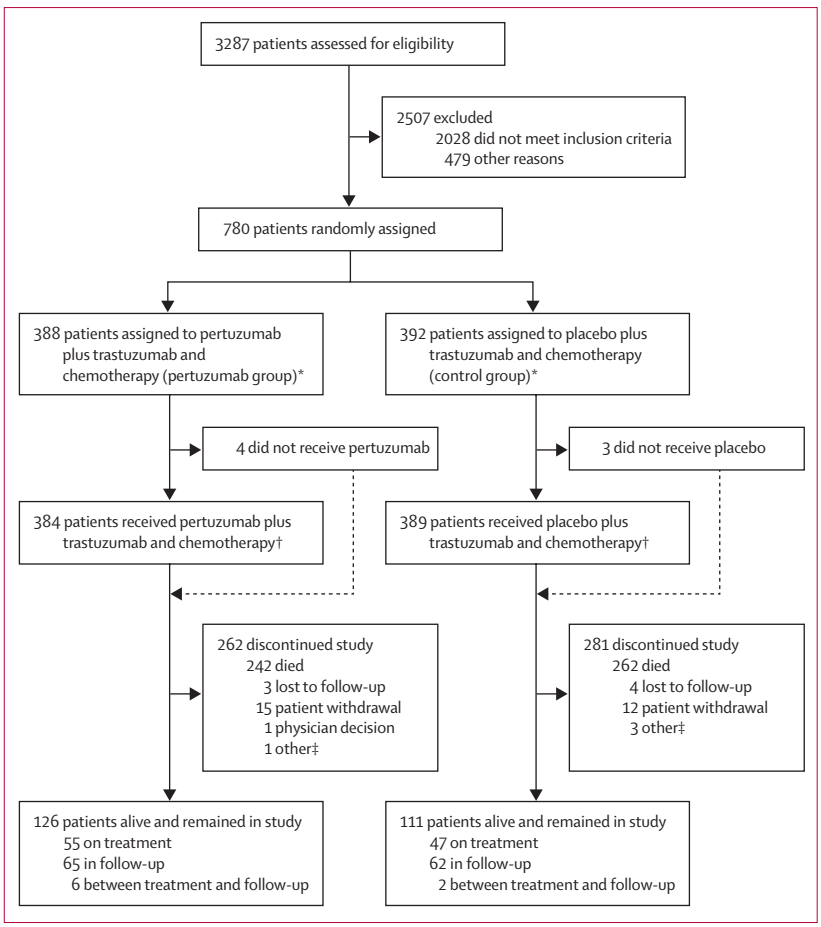


Figure 1: **Trial profile**
*Intention-to-treat population. †One patient assigned to the placebo group received one dose of pertuzumab in error and was included in the safety population for the pertuzumab group; final safety population: pertuzumab (n=385), placebo (n=388). ‡These patients were enrolled in the study but were subsequently identified as ineligible and discontinued study participation without receiving any study treatment.

Statistical analysis

We calculated a target enrolment of 780 patients (390 per treatment group) based on the target hazard ratio (HR) of 0·777 and an assumed median overall survival of 15·0 months in the placebo group *vs* 19·3 months in the pertuzumab group (calculation based on data from the ToGA trial).[5] With 502 overall survival events, we expected the study to have 80% power to detect a significant difference in overall survival (two-sided α=0·05). The minimum detectable difference corresponded to an HR of 0·836. We planned one interim efficacy analysis at about 70% information fraction. We determined the interim efficacy analysis boundary by applying the Lan-DeMets method and an O'Brien–Fleming α-spending function, which resulted in a two-sided significance level of 0·0148 for the interim analysis (with 351 deaths) and 0·0455 for the final analysis (with 504 deaths).

We assessed overall survival and progression-free survival in the intention-to-treat (ITT) population, defined as all patients randomly assigned to a treatment group regardless of whether they received a study drug, analysed according to group allocation. We assessed overall survival in predefined subgroups based on age, race, stratification factors, and other potential baseline prognostic factors. We censored patients who were still alive at the time of data cutoff at the last date of or before cutoff. We censored patients who did not have any data after baseline at the date of randomisation plus 1 day. For the assessment of progression-free survival and duration of objective response, we censored patients who did not have documented progressive disease or death at the date of tumour assessment on which the patient was last known to be progression-free before the clinical cutoff date. For the assessment of progression-free survival, we censored patients who did not have any tumour assessment data after baseline at the date of randomisation plus 1 day. We assessed overall response and clinical benefit in patients in the ITT population who had measurable disease at baseline. Patients who did not have any tumour assessment data after baseline were counted as non-responders. We assessed safety outcomes in all randomly assigned patients who received at least one dose of study treatment (analysed according to treatment received). We assessed patient-reported outcomes in the ITT population that had a baseline patient-reported outcome assessment and at least one assessment after baseline. We assessed changes in HRQoL, gastric cancer disease-related symptoms, and patient-reported treatment-related symptoms using the mean change of linear transformed scores from baseline, with a 10-point or greater change in score being perceived by patients as clinically meaningful.[15]

We estimated median overall survival for treatment groups (with 95% CIs) using the Kaplan–Meier approach; we computed 95% CIs using the Brookmeyer and Crowley method. We used a stratified two-sided log-rank test to compare overall survival in the two treatment groups and a stratified Cox proportional hazards regression model to estimate the HR between treatment groups with 95% CI, using the stratification factors geographical region, HER2 status, and previous gastrectomy. We did sensitivity analyses using the unstratified log-rank test, stratified and unstratified log-rank tests using the data collected from the IxRS system rather than the electronic case report form, and we also did a Kaplan–Meier estimate of time-to-censoring in treatment groups. We pooled small strata with fewer than 20 patients in the stratified analysis in line with the statistical analysis plan. We did no formal testing of the proportional hazards model. We used a similar approach to that for overall survival to estimate median progression-free survival. We summarised the proportion of patients who achieved an overall response and clinical benefit in each treatment group and calculated 95% CIs using the Clopper–Pearson method. We estimated median duration of objective response using the Kaplan–Meier method (we computed 95% CI using the Brookmeyer and Crowley method). We implemented a hierarchical testing procedure for the analysis of the primary endpoint (overall

survival) and two secondary endpoints (progression-free survival and objective response). We estimated median TTD with the Kaplan–Meier method. We censored patients without deterioration at the time of completing the last questionnaire.

We used SAS version 9.2 and 9.4 for statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT01774786.

Role of the funding source

This study was sponsored by F. Hoffmann-La Roche, Ltd (Basel, Switzerland). The funder provided the study drugs and the funder and its employees were involved in study design, protocol development, regulatory and ethics approvals, study conduct and management, safety monitoring and reporting, data management, data analysis, and data interpretation. All authors had access to the study data, were involved in the data analysis and interpretation, contributed to the writing of the manuscript, and approved the final version for submission. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Between June 10, 2013, and Jan 12, 2016, 3287 patients were screened for eligibility. Of these, 780 eligible patients were randomly assigned to receive pertuzumab plus trastuzumab and chemotherapy (pertuzumab group, n=388) or placebo plus trastuzumab and chemotherapy (control group, n=392), constituting the ITT population (figure 1). Of the patients randomly assigned, seven did not receive the assigned study treatment (four in the pertuzumab group; three in the control group) and one patient assigned to the control group received both treatments in error and was counted in the pertuzumab group for safety analyses. Therefore, 385 patients in the pertuzumab group and 388 patients in the control group were evaluated for safety. The data cutoff for the primary analysis of overall survival was Dec 9, 2016. Median duration of overall survival follow-up was 24·4 months (95% CI 22·3–26·1) in the pertuzumab group and 25·0 months (22·3–28·9) in the control group.

Baseline patient demographics and disease characteristics were generally well balanced between treatment groups (table 1). Most patients in both treatment groups had intestinal subtype gastric cancer, with the primary tumour located in the stomach. Approximately two-thirds of patients in each treatment group had a HER2 immunohistochemistry score of 3+.

Mean number of pertuzumab or placebo and trastuzumab treatment cycles per patient was 13·1 (SD 10·7) in the pertuzumab group and 11·2 (10·0) in the control group; mean relative dose intensity was similar in the two treatment groups (appendix p 13). Mean relative dose intensity for capecitabine and cisplatin chemotherapies was numerically lower in the pertuzumab than in the control group; however, the number of cycles of chemotherapy was similar across treatment groups (appendix p 13). 41 (41%) of 100 patients in the pertuzumab group and 29 (28%) of 103 patients in the control group had at least one dose modification in 5-fluorouracil; 194 (65%) of 300 patients in the pertuzumab group and 164 (54%) of 301 patients in the control group had at least one dose modification in capecitabine; and 106 (28%) of 382 patients in the pertuzumab group and 74 (19%) of 388 patients in the control group had at least one dose modification in cisplatin. The denominators refer to the number of

	Pertuzumab group (n=388)	Control group (n=392)
Sex		
Male	294 (76%)	323 (82%)
Female	94 (24%)	69 (18%)
Age, years		
Median (IQR)	62·0 (54·5–69)	61·0 (54–68)
Geographic region		
Asia (excluding Japan)	143 (37%)	146 (37%)
Japan	40 (10%)	40 (10%)
North America, western Europe, Australia	133 (34%)	133 (34%)
South America, eastern Europe	72 (19%)	73 (19%)
Measurability		
Measurable disease	351 (91%)	352 (90%)
Non-measurable evaluable disease only	37 (10%)	40 (10%)
Number of metastatic sites*		
1–2	305 (79%)	303 (78%)
>2	83 (21%)	88 (23%)
Histological subtypes (Lauren classification)		
Diffuse	18 (5%)	21 (5%)
Intestinal	353 (91%)	350 (89%)
Other†	17 (4%)	21 (5%)
Primary site		
Gastro-oesophageal junction	110 (28%)	98 (25%)
Stomach	278 (72%)	294 (75%)
ECOG performance status*		
0	162 (42%)	162 (41%)
1	226 (58%)	229 (59%)
HER2 status		
IHC 2+ and ISH-positive	129 (33%)	130 (33%)
IHC 3+	259 (67%)	262 (67%)
Previous gastrectomy		
Yes	105 (27%)	102 (26%)
No	283 (73%)	290 (74%)

Data are n (%), unless otherwise specified. ECOG= Eastern Cooperative Oncology Group. IHC=immunohistochemistry. ISH=in-situ hybridisation. *n=391 in the control group. †Mixed or indeterminable.

Table 1: **Baseline demographics and disease characteristics (intention-to-treat population)**

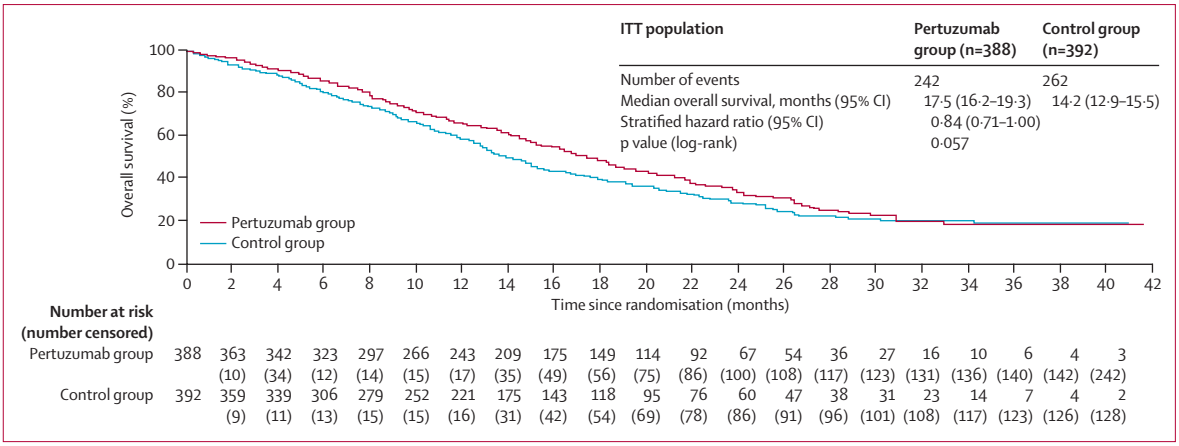


Figure 2: **Overall survival in the ITT population**
ITT=intention-to-treat. HR=hazard ratio.

patients who received each type of chemotherapy (capecitabine, 5-fluorouracil, and cisplatin).

The number of patients receiving at least one anticancer therapy after treatment, during the course of the study, was similar between treatment groups (165 [43%] of 388 patients in the pertuzumab group and 165 [42%] of 392 patients in the control group; appendix p 14). Ramucirumab was received by 19 (5%) of 388 patients in the pertuzumab group and 23 (6%) of 392 patients in the control group.

At clinical cutoff, in the ITT population 242 (62%) of 388 patients in the pertuzumab group and 262 (67%) of 392 patients in the control group had died. The difference in overall survival between the two treatment groups was not significant (HR 0·84 [95% CI 0·71–1·00]; p=0·057; figure 2). Median overall survival was 17·5 months (95% CI 16·2–19·3) in the pertuzumab group compared with 14·2 months (12·9–15·5) in the control group. The sensitivity analyses were consistent with the primary analysis (data not shown). Most subgroups analysed had overall survival HRs consistent with the ITT population (figure 3).

The addition of pertuzumab to trastuzumab and chemotherapy was associated with an improvement in progression-free survival (HR 0·73 [95% CI 0·62–0·86]; p=0·0001; this efficacy analysis was descriptive only as the primary endpoint was not met]). Median progression-free survival was 8·5 months (95% CI 8·2–9·7) in the pertuzumab group compared with 7·0 months (6·4–8·2) in the control group (figure 4). The proportion of patients who achieved an objective response was larger in the pertuzumab group (56·7% [95% CI 51·3–62·0]) than in the control group (48·3% [43·0–53·7]; difference 8·4% [0·9–15·9]; χ^2 p=0·026). However, we could not assess significance for progression-free survival and objective response because of the hierarchical testing procedure used, meaning that these analyses were purely descriptive in nature. Median duration of objective response was longer in the pertuzumab group (10·2 months [95% CI 8·4–10·7]) than in the control group (8·4 months [6·8–8·7]). The proportion of patients who achieved a clinical benefit was 84·6% (95% CI 80·4–88·2) in the pertuzumab group and 81·3% (76·8–85·2) in the placebo group (difference 3·37 [95% CI –2·34 to 9·07]; p=0·24).

Adverse events were reported in 381 (99%) of 385 patients in the pertuzumab group and 385 (99%) of 388 patients in the control group; serious adverse events occurred in 175 (45%) patients in the pertuzumab group versus 152 (39%) in the control group, and grade 3–5 adverse events occurred in 307 (80%) patients in the pertuzumab group versus 282 (73%) patients in the control group (appendix pp 15–25). Diarrhoea was the most common serious adverse event in both groups (17 [4%] patients in the pertuzumab group vs 20 [5%] patients in the control group). Frequency of the most common adverse events of grade 3 or worse were generally similar between treatment groups (table 2). The most common grade 3–5 adverse events were neutropenia (116 [30%] patients in the pertuzumab group *vs* 108 [28%] patients in the control group), anaemia (56 [15%] *vs* 65 [17%]), and diarrhoea (51 [13%] *vs* 25 [6%]). Adverse events of grade 3 or worse with approximately 5% or greater difference in incidence between the pertuzumab and control groups were diarrhoea, hypokalaemia, and nausea (table 2). No patients discontinued pertuzumab due to diarrhoea. Adverse events leading to the discontinuation of pertuzumab and trastuzumab or placebo and trastuzumab were reported in 45 (12%) of 385 patients in the pertuzumab group and 45 (12%) of 388 patients in the control group. Serious adverse events that the investigator considered to be related to study treatment were reported in 48 (12%) patients in the pertuzumab group and 40 (10%) patients in the control group.

At the time of clinical cutoff, 502 patients (240 in the pertuzumab group and 262 in the control group) in the safety population had died during the study (two additional patients included in the ITT population died without

receiving treatment). Most deaths were related to disease progression (213 [89%] of 240 in the pertuzumab group and 232 [89%] of 262 in the control group). Adverse events leading to death were reported in 27 (7%) of 385 patients in the pertuzumab group and 30 (8%) of 388 patients in the control group (appendix p 25). Of these, seven deaths were considered by the investigator to be related to treatment (multiple organ failure, pulmonary embolism, haemodynamic instability, and unexplained death in one patient each, and septic shock in three patients), all of which occurred in the control group.

Rates of symptomatic LVSD were low overall and similar between treatment groups (table 3). Two symptomatic LVSD events were reported in the pertuzumab group (both grade 3 adverse events; one New York Heart Association [NYHA] class II, one NYHA class III). One symptomatic LVSD event was reported in the control group (no NYHA class recorded).

	Pertuzumab group (n=388)		Control group (n=392)		HR (95% CI)
	n/N	Median, months (95% CI)	n/N	Median, months (95% CI)	
Sex					
Men	181/294	18·1 (16·4–19·9)	210/323	14·9 (13·2–16·7)	0·88 (0·72–1·07)
Women	61/94	16·2 (12·9–21·8)	52/69	12·3 (9·2–13·5)	0·67 (0·46–0·98)
Race					
Asian	112/182	19·3 (16·4–21·8)	123/188	16·7 (14·8–19·2)	0·84 (0·65–1·08)
White	120/191	16·4 (14·1–18·8)	126/187	12·7 (10·7–13·8)	0·86 (0·67–1·10)
Other	6/9	10·1 (7·3–24·2)	12/15	4·9 (2·3–14·1)	0·64 (0·24–1·72)
Region					
Asia (excluding Japan)	89/143	18·3 (15·4–21·3)	92/146	17·3 (14·8–20·6)	0·93 (0·70–1·25)
Japan	24/40	22·0 (15·2–NA)	30/40	15·6 (10·7–19·2)	0·65 (0·38–1·11)
North America, western Europe, Australia	82/133	17·4 (12·7–22·1)	88/133	13·0 (11·4–15·1)	0·87 (0·64–1·17)
South America, eastern Europe	47/72	16·4 (11·5–18·9)	52/73	11·7 (9·1–13·5)	0·80 (0·54–1·19)
HER2 status					
IHC 2+ and ISH-positive	89/129	13·0 (10·7–15·9)	99/130	11·9 (10·1–13·2)	0·82 (0·61–1·09)
IHC 3+	153/259	19·1 (17·5–22·2)	163/262	17·1 (14·7–20·3)	0·86 (0·69–1·07)
Previous gastrectomy					
Yes	53/105	19·3 (17·5–24·2)	59/102	17·1 (14·5–22·4)	0·86 (0·59–1·25)
No	189/283	16·4 (14·8–18·6)	203/290	13·2 (12·3–15·1)	0·83 (0·68–1·02)
Measurability					
Measurable disease	218/351	17·4 (15·9–19·5)	239/352	14·2 (12·9–15·7)	0·84 (0·70–1·01)
Non-measurable evaluable disease only	24/37	18·7 (14·5–23·7)	23/40	14·5 (11·4–NA)	0·86 (0·48–1·52)
ECOG performance status at baseline					
0	100/162	18·3 (16·4–21·8)	96/162	19·4 (15·1–22·4)	1·02 (0·77–1·36)
1	142/226	16·6 (14·5–19·9)	166/229	12·9 (11·7–13·8)	0·74 (0·59–0·92)
Previous adjuvant and/or neoadjuvant chemotherapy and/or radiotherapy					
Yes	26/55	23·0 (18·7–NA)	32/53	14·7 (12·7–21·8)	0·71 (0·42–1·19)
No	216/333	16·6 (15·0–18·6)	230/339	13·8 (12·8–15·5)	0·87 (0·72–1·04)
Number of metastatic sites					
1–2	186/305	18·5 (15·9–20·3)	196/303	15·1 (13·7–17·6)	0·87 (0·71–1·07)
>2	56/83	16·4 (14·1–19·3)	66/88	10·6 (7·9–12·8)	0·75 (0·52–1·07)
Number of lesions at baseline					
≤4	138/244	19·5 (17·0–22·2)	133/215	14·8 (13·2–17·2)	0·84 (0·66–1·06)
>4	104/144	15·0 (12·3–17·5)	129/175	13·0 (10·6–15·6)	0·90 (0·70–1·17)
Primary site					
Gastro-oesophageal junction	55/110	23·3 (16·6–30·8)	60/98	14·7 (12·8–22·0)	0·76 (0·53–1·10)
Stomach	187/278	16·7 (15·1–18·7)	202/294	13·8 (12·5–15·7)	0·87 (0·72–1·07)
Gastric cancer type					
Diffuse	15/18	10·7 (8·1–15·2)	16/21	6·5 (4·0–11·8)	0·82 (0·40–1·69)
Intestinal	215/353	18·5 (16·5–20·3)	228/350	14·9 (13·2–17·2)	0·85 (0·71–1·02)
Mixed	11/16	15·9 (9·6–23·9)	17/19	10·3 (8·4–13·5)	0·60 (0·28–1·29)
All patients	**242/388**	**17·5 (16·2–19·3)**	**262/392**	**14·2 (12·9–15·5)**	**0·84 (0·71–1·00)**

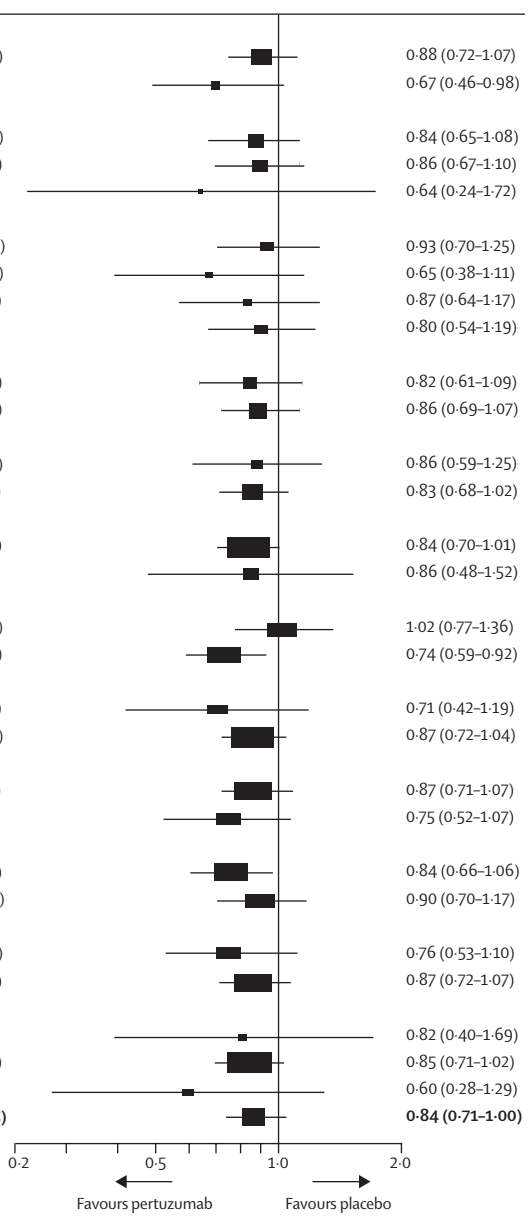
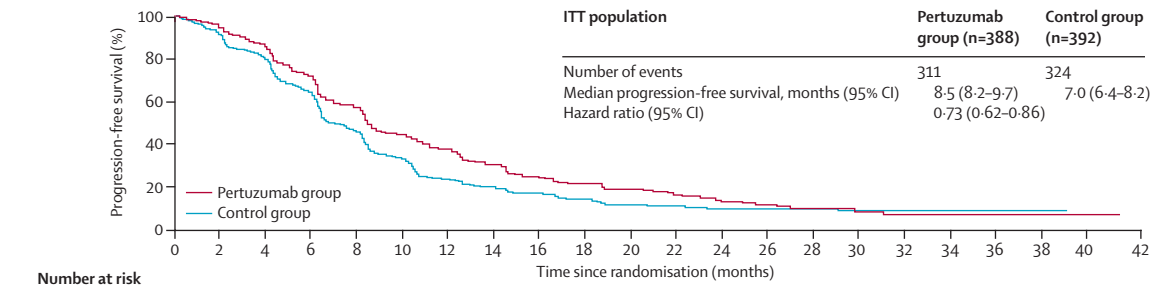


Figure 3: **Subgroup analysis of overall survival**
n represents the number of patients with an event and N is the number of patients in the individual subgroup. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. IHC=immunohistochemistry. ISH=in-situ hybridisation. NA=not assessed.

High completion rates for the patient-reported outcome questionnaires were achieved in both treatment groups throughout the study: more than 90% completion in both treatment groups for all cycles (data not shown). No clinically meaningful differences were detected between groups in overall HRQoL (figure 5) or the median TTD in abdominal pain, appetite loss, eating restrictions, or fatigue symptoms (both TTD1 and TTD2;



Number at risk (number censored)

Pertuzumab group	388	354 (13)	320 (13)	267 (16)	213 (17)	165 (18)	135 (21)	104 (29)	80 (34)	67 (38)	50 (46)	36 (55)	26 (58)	18 (64)	14 (65)	7 (71)	4 (73)	2 (75)	2 (75)	2 (75)	NE
Control group	392	349 (10)	301 (14)	242 (15)	172 (17)	120 (21)	85 (22)	67 (29)	51 (35)	35 (43)	27 (46)	21 (50)	17 (52)	15 (54)	12 (57)	8 (60)	7 (61)	4 (64)	1 (67)	1 (67)	NE

Figure 4: **Progression-free survival in the ITT population**
Stratified hazard ratio. Progression-free survival was investigator-assessed. ITT=intention-to-treat. NE=not evaluable.

	Pertuzumab group (n=385)				Control group (n=388)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	189 (49%)	36 (9%)	0	0	202 (52%)	17 (4%)	1 (0%)	0
Diarrhoea	186 (48%)	49 (13%)	2 (1%)	0	111 (29%)	24 (6%)	0	1 (0%)
Vomiting	122 (32%)	25 (7%)	0	0	104 (27%)	21 (5%)	1 (0%)	0
Stomatitis	67 (17%)	15 (4%)	0	0	60 (16%)	9 (2%)	0	0
Constipation	53 (14%)	0	0	0	82 (21%)	2 (1%)	0	0
Abdominal pain	40 (10%)	5 (1%)	0	0	46 (12%)	5 (1%)	0	0
Neutropenia	86 (22%)	102 (27%)	14 (4%)	0	95 (25%)	94 (24%)	14 (4%)	0
Anaemia	103 (27%)	54 (14%)	2 (1%)	0	85 (22%)	59 (15%)	5 (1%)	1 (0%)
Leukopenia	55 (14%)	20 (5%)	2 (1%)	0	49 (13%)	18 (5%)	2 (1%)	0
Thrombocytopenia	47 (12%)	9 (2%)	5 (1%)	0	57 (15%)	12 (3%)	4 (1%)	0
Febrile neutropenia	0	4 (1%)	6 (2%)	0	1 (0%)	8 (2%)	3 (1%)	0
Fatigue	118 (31%)	23 (6%)	0	0	105 (27%)	17 (4%)	0	0
Asthenia	43 (11%)	15 (4%)	1 (0%)	0	48 (12%)	14 (3%)	0	0
Pyrexia	54 (14%)	2 (1%)	0	0	56 (14%)	1 (0%)	0	0
Mucosal inflammation	30 (8%)	12 (3%)	1 (0%)	0	24 (6%)	12 (3%)	0	0
Death	0	0	0	8 (2%)	0	0	0	9 (2%)
Decreased appetite	142 (37%)	38 (10%)	1 (0%)	0	136 (35%)	26 (7%)	0	0
Hypokalaemia	34 (9%)	33 (9%)	9 (2%)	0	24 (6%)	16 (4%)	6 (2%)	0
Hyponatraemia	11 (3%)	6 (2%)	1 (0%)	0	9 (2%)	18 (5%)	3 (1%)	0
Dehydration	12 (3%)	10 (3%)	1 (0%)	0	9 (2%)	11 (3%)	0	0
Weight loss	69 (18%)	6 (2%)	0	0	46 (12%)	3 (1%)	0	0
Reduced creatinine renal clearance	66 (17%)	5 (1%)	0	0	48 (12%)	3 (1%)	0	0
Palmar–plantar erythrodysaesthesia syndrome	76 (20%)	9 (2%)	0	0	87 (22%)	11 (3%)	0	0
Pneumonia	7 (2%)	8 (2%)	0	3 (1%)	7 (2%)	5 (1%)	2 (1%)	1 (0%)
Infusion-related reaction	47 (12%)	0	0	0	24 (6%)	1 (0%)	0	0
Insomnia	31 (8%)	1 (0%)	0	0	43 (11%)	1 (0%)	0	0

Data are n (%). For frequency counts by preferred term, multiple occurrences of the same adverse event in an individual are counted only once. For frequency counts of grade 1–2 adverse events, multiple occurrences of the same adverse event in an individual are counted separately. Adverse events listed in order of most common any-grade adverse events per system organ class in the pertuzumab group. *Any grade 1–2 adverse event occurring in ≥10% of patients in either treatment group, and all grade 3, 4, and 5 adverse events occurring in ≥2% of patients in either treatment group are listed. A table of all adverse events is in the appendix (pp 15–25).

Table 2: **Adverse event by grade***

table 4); the median TTD1 or TTD2 was not reached for any of these symptoms, except for fatigue (table 4). Clinically meaningful (≥10-point change in score from baseline) worsening in diarrhoea and taste sensation were observed in the pertuzumab group (appendix p 12).

Discussion

This multinational double-blind, randomised, placebo-controlled phase 3 trial investigating the efficacy and safety of adding pertuzumab to trastuzumab in first-line therapy for HER2-positive metastatic gastric cancer or gastro-oesophageal junction cancer did not meet its primary endpoint of showing a significant improvement in overall survival. The HR for overall survival was consistent across patient subgroups. We observed a trend towards therapeutic activity for the key secondary endpoints of progression-free survival and the proportion of patients who achieved an objective response with the addition of pertuzumab, but we could not assess statistical significance because of hierarchical testing.

Safety was generallly similar between the treatment groups, with the exception of increased rates of grade 3 or worse diarrhoea, hypokalaemia, and nausea adverse events in the pertuzumab versus control group. Increased rates of diarrhoea were observed in the pertuzumab group compared with the control group, although none of these events led to the discontinuation of pertuzumab. However, the relative dose intensity of chemotherapy treatment was numerically reduced in the pertuzumab group as compared with the placebo control group. In terms of cardiac safety, LVSD was generally low and similar between groups. No new or unexpected safety events were reported, which is important given that the dose of 840 mg pertuzumab every 3 weeks assessed in the JACOB trial was double the maintenance dose currently approved for breast cancer treatment.

More dose modifications and interruptions in chemotherapy treatment occurred in the pertuzumab group compared with the placebo group. This difference might be related to overlapping toxic effects, such as diarrhoea, which is thought to be associated with both pertuzumab and capecitabine. However, the overall number of chemotherapy treatment cycles and the small difference in relative dose intensity between groups suggests that this observation might not be clinically meaningful. Moreover, interpretation of the dose modifications or

	Pertuzumab group (n=385)	Control group (n=388)
Patients with symptomatic LVSD	2 (1%)	1 (<1%)*
NYHA class III or IV	1 (<1%)	0
NYHA class II	1 (<1%)	0
Patients with asymptomatic LVSD	18 (5%)	17 (4%)
Mean baseline visit LVEF (range)	64·8% (52·0–84·0)	64·9% (51·0–87·0)
Post-baseline LVEF value and change from baseline	n=333	n=331
Patients with decrease from baseline of ≥10 percentage points and to <50%	18 (5%)	16 (5%)
Patients with confirmed LVEF decline†	7 (2%)	7 (2%)

Data are n (%), unless otherwise specified. LVEF=left ventricular ejection fraction. LVSD=left ventricular systolic dysfunction. NYHA=New York Heart Association. *No NYHA class reported for this single event. †Confirmed LVEF declines were defined as LVEF decrease from baseline of ≥10 percentage points and to <50% at two consecutive visits.

Table 3: **Cardiac safety**

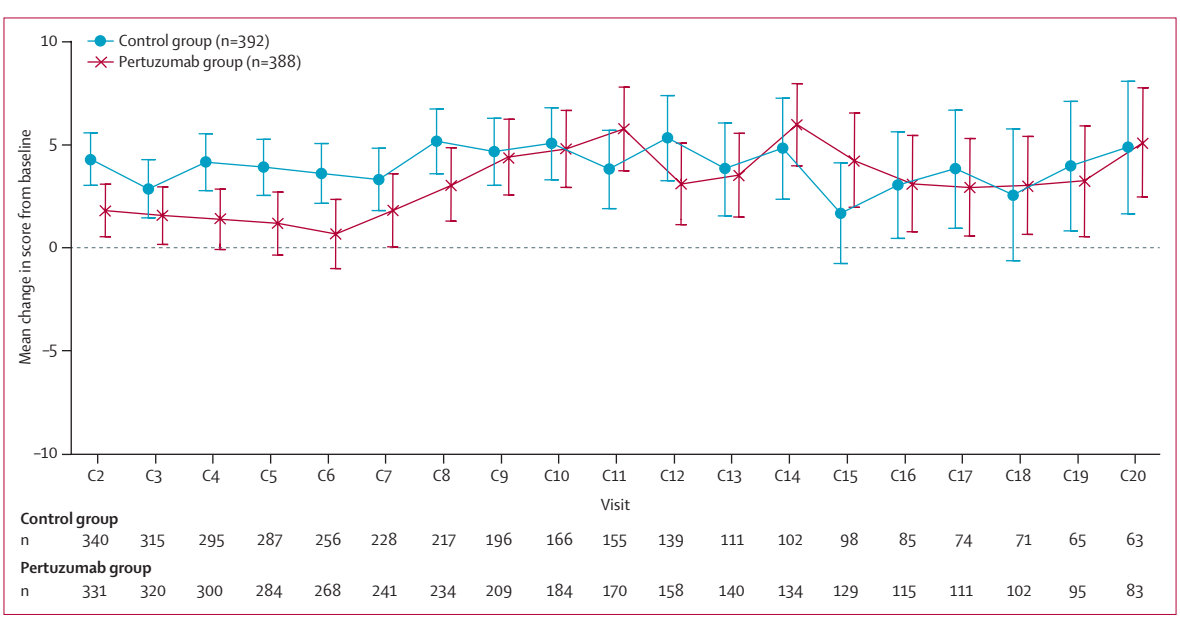


Figure 5: **Patient-reported outcomes, mean change from baseline in Global Health Status scale (EORTC QLQ-C30)**
Baseline is defined as cycle 1, day 1. Error bars represent SE of the mean. Only visits that yielded data for ≥50 patients in both treatment groups are presented. Higher scores in the Global Health Status scale represent higher levels of functioning. C=cycle. EORTC QLQ= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire.

	Pertuzumab group	Control group	Stratified HR (95% CI)
TTD1			
Abdominal pain*	n=367	n=373	
Patients with events	72 (20%)	73 (20%)	0·98 (0·71–1·37)
Median TTD1, months	NE	NE	
Appetite loss symptom scale†	n=371	n=383	
Patients with events	147 (40%)	132 (35%)	1·13 (0·89–1·44)
Median TTD1, months	NE (7·4–NE)	NE (15·0–NE)	
Eating restrictions*	n=366	n=373	
Patients with events	119 (33%)	102 (27%)	1·15 (0·88–1·50)
Median TTD1, months	NE (16·8–NE)	NE (17·1–NE)	
Fatigue symptom scale†	n=372	n=383	
Patients with events	191 (51%)	184 (48%)	1·06 (0·86–1·30)
Median TTD1, months	3·91 (3·02–6·87)	4·90 (3·45–8·71)	
TTD2			
Abdominal pain*	n=180	n=164	
Patients with events	36 (20%)	34 (20%)	0·96 (0·59–1·55)
Median TTD2, months	NE	NE	
Appetite loss symptom scale†	n=181	n=166	
Patients with events	29 (16%)	31 (19%)	0·78 (0·46–1·32)
Median TTD1, months	NE	NE	
Eating restrictions*	n=180	n=162	
Patients with events	29 (16%)	21 (13%)	1·27 (0·71–2·28)
Median TTD1, months	NE	NE	
Fatigue symptom scale†	n=181	n=166	
Patients with events	53 (29%)	49 (30%)	0·90 (0·60–1·36)
Median TTD1, months	NE (13·6–NE)	17·3 (11·4–NE)	

Data are n (%) or median time to deterioration (95% CI). Deterioration is defined as score increase of ≥10 points for at least two consecutive cycles or an initial score increase of ≥10 points followed by death within 3 weeks. EORTC QLQ=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire. EORTC QLQ-STO22=EORTC QLQ gastric cancer module. HR=hazard ratio. NE=not evaluable. TTD=time to deterioration. *Abdominal pain and eating restrictions assessed using the EORTC QLQ–STO22 questionnaire. †Appetite loss and fatigue symptoms assessed using the EORTC QLQ-C30 questionnaire.

Table 4: **Patient-reported outcomes**

interruptions data might be confounded by the observed increase in treatment duration for both pertuzumab and chemotherapy in some patients. The increased number of dose modifications or interruptions in chemotherapy treatment observed in the pertuzumab group might also have played a part in the study outcome.

Data from patient-reported outcome questionnaires collected throughout the study indicated that pertuzumab in addition to trastuzumab plus chemotherapy was not associated with clinically meaningful differences in HRQoL or gastric cancer symptoms. The clinically meaningful worsening in diarrhoea that was reported in the pertuzumab group occurred during cycles 2–7, consistent with the higher rates of diarrhoea observed in the pertuzumab group coinciding with the period when chemotherapy was given with anti-HER2 antibodies (cycles 1–6; appendix p 12).

Differences in the underlying biology between HER2-positive metastatic gastric cancer and HER2-positive breast cancer might help explain why the JACOB trial did not meet its primary endpoint, because these differences could affect the therapeutic activity of HER2-targeted drugs in different cancers. Gastric tumours more frequently show heterogeneous HER2 immunohistochemical staining patterns, lower HER2 expression concentration, and incomplete membrane staining as compared with breast cancer,[11,16] which could influence the treatment activity of HER2-targeted drugs. HER2 overexpression levels might differ between the primary and metastatic tumours in an individual patient: a small retrospective analysis has suggested a discordance rate of 9% between primary gastric cancer tumours and lymph node metastases,[17] although similar discrepancies have also been described in breast cancer so this does not seem a likely explanation for the results in our study.[18] The proportion of HER2-positive tumours that are driven predominantly by the HER2 signalling pathway might differ between HER2-positive metastatic gastric cancer and HER2-positive breast cancer; such potential differences could explain the strong association between HER2 positivity and poorer outcomes in breast cancer[19] as compared with the less clear prognostic value of HER2 in gastric cancer.[2–4] Further research to better identify those patients with HER2-driven gastric cancer who might benefit more from HER2-targeted therapies is needed.

Several phase 3 studies have investigated the optimal use of anti-HER2 drugs in HER2-positive advanced gastric cancer. Investigation of a higher dose of trastuzumab in patients with poor prognostic factors at baseline has confirmed the approved dose of trastuzumab for all patients with gastric cancer.[20] However, trials of other HER2-directed drugs—including lapatinib plus capecitabine or oxaliplatin in the first-line setting[21] and the use of trastuzumab emtansine in patients who progressed after first-line therapy with trastuzumab[22]—have not met their primary endpoints. Although trials of lapatinib and trastuzumab emtansine have not shown improved overall survival in gastric cancer, both drugs are currently approved for use in patients with HER2-overexpressing metastatic breast cancer,[23–26] further highlighting the differences in therapeutic responses to HER2-targeted therapies in gastric cancer versus breast cancer. Together, these negative trials suggest that oncogenic drivers beyond HER2 are crucial in identifying and targeting therapies for metastatic gastric cancer or gastro-oesophageal junction cancer.

The JACOB study, which to our knowledge is one of the largest randomised phase 3 studies in HER2-positive gastric cancer so far, has a number of potential limitations. The study was not powered to assess efficacy endpoints in clinical and biomarker subgroups and there was no multiplicity control for subgroup analyses, so we cannot assess which patients might be more likely to benefit from pertuzumab treatment. Although this study used a cisplatin-based doublet regimen (as used in ToGA),[5] re-examination of the optimal cytotoxic chemotherapy backbone for use with anti-HER2 drugs might be valuable.

A meta-analysis[27] suggested that use of trastuzumab plus oxaliplatin and capecitabine or 5-fluorouracil in the first-line setting might be associated with improved overall survival in patients with advanced oesophagogastric cancer, and might be better tolerated compared with the cisplatin-based doublet chemotherapy.[5] However, use of trastuzumab and oxaliplatin is unlikely to have led to a different result given the design of the trial.

In conclusion, despite the suggestion of treatment activity, the addition of pertuzumab to trastuzumab and chemotherapy did not show an improvement in overall survival in patients with HER2-positive metastatic gastric cancer or gastro-oesophageal junction cancer compared with placebo plus trastuzumab and chemotherapy. Pertuzumab plus trastuzumab and chemotherapy had a similar safety profile to trastuzumab and chemotherapy, except for the increased incidence of diarrhoea, which was clinically manageable and did not lead to pertuzumab treatment discontinuations. In view of the multinational recruitment of patients in this trial and overall adherence to the protocol, the results of this trial are considered generalisable to patients with HER2-positive metastatic gastric cancer. Our study adds to current evidence suggesting that there are intrinsic differences in the tumour biology of HER2-positive advanced gastric cancer and HER2-positive breast cancer, including potential differences in the role of HER2 in driving disease progression. Further studies are needed to identify first-line treatment options to improve patient outcomes in HER2-positive advanced gastric cancer and to better identify patients who might benefit from dual anti-HER2 targeted regimens.

Contributors

JT contributed to the literature search. HW contributed to the provision and development of figures. JT, LS, AO, MAS, JE-W, PMH, and KYK designed the study. JT, LS, AO, MAS, PMH, and KYK were involved in patient recruitment. JT, LS, MAS, KC, PMH, and KYK contributed to data collection. JT, MAS, KC, CS, HW, JE-W, KK, PMH, and KYK analysed data. AO, MAS, KC, CS, HW, JE-W, KK, JT, PMH, and KYK interpreted data. All authors approved the final version of the manuscript.

Declaration of interests

JT reports advisory board membership for Bayer, Boehringer Ingelheim, Genentech/Roche, Lilly, Merck Sharp and Dohme, Merck Serono, Novartis, Roche, Sanofi, Symphogen, and Taiho outside of the submitted work. AO reports grants from BMS. HW is an employee of Roche China Holding Ltd and reports stock ownership in F. Hoffmann-La Roche, Ltd. KYK reports grants from Roche, personal fees from Ono, BMS, Novartis, and Lilly outside of the submitted work, and grants and personal fees from Daehwa and LSK Biopharma outside of the submitted work. KC, KK, and JE-W are employees of Genentech, Inc. CS is an employee of F. Hoffmann-La Roche, Ltd, and CS and KK report stock ownership in F. Hoffmann-La Roche, Ltd. PMH reports grants from Roche, related to this study. LS and MAS declare no competing interest.

Acknowledgments

We thank all the investigators, clinicians, and research staff who supported this trial, the patients who participated in the trial, and their families. We acknowledge Tiffanie Chan for her scientific review of the draft manuscript and the contributions and support from the members of the Cardiac Review Committee and Independent Data Monitoring Committee (see appendix for the full list of committee members). Support for third-party medical writing assistance for this manuscript, furnished by Rachel Johnson and Daniel Clyde of Health Interactions was provided by F. Hoffmann-La Roche, Ltd.

References

1 WHO International Agency for Research on Cancer. Cancer fact sheets: stomach cancer. http://gco.iarc.fr/today/fact-sheets-cancers?cancer=5&type=0&sex=0 (accessed Jan 9, 2018).
2 Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008; **19:** 1523–29.
3 Lei YY, Huang JY, Zhao QR, et al. The clinicopathological parameters and prognostic significance of HER2 expression in gastric cancer patients: a meta-analysis of literature. *World J Surg Oncol* 2017; **15:** 68.
4 Ock CY, Kim TY, Lee KH, et al. Metabolic landscape of advanced gastric cancer according to HER2 and its prognostic implications. *Gastric Cancer* 2016; **19:** 421–30.
5 Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376:** 687–97.
6 Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27:** v38–49.
7 National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN guidelines): gastric cancer. https://www.nccn.org/professionals/physician_gls/default.aspx (accessed Jan 9, 2018).
8 von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017; **377:** 122–31.
9 Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; **366:** 109–19.
10 Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; **372:** 724–34.
11 Rüschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. *Mod Pathol* 2012; **25:** 637–50.
12 Kang YK, Rha SY, Tassone P, et al. A phase IIa dose-finding and safety study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2-positive advanced gastric cancer. *Br J Cancer* 2014; **111:** 660–66.
13 Cortés J, Swain SM, Kudaba I, et al. Absence of pharmacokinetic drug-drug interaction of pertuzumab with trastuzumab and docetaxel. *Anticancer Drugs* 2013; **24:** 1084–92.
14 Kirschbrown WP, Wang B, Nijem I, et al. Pharmacokinetic (PK) and exposure-response (ER) analysis of pertuzumab (P) in patients (pts) with HER2-positive metastatic gastroesophageal junction and gastric cancer (mGEJC/GC). *J Clin Oncol* 2018; **36**(suppl)**:** 2564 (abstr).
15 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16:** 139–44.
16 Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 2008; **52:** 797–805.
17 Ieni A, Barresi V, Caltabiano R, et al. Discordance rate of HER2 status in primary gastric carcinomas and synchronous lymph node metastases: a multicenter retrospective analysis. *Int J Mol Sci* 2014; **15:** 22331–41.
18 Peng Z, Zou J, Zhang X, et al. HER2 discordance between paired primary gastric cancer and metastasis: a meta-analysis. *Chin J Cancer Res* 2015; **27:** 163–71.
19 Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987; **235:** 177–82.
20 Shah MA, Xu RH, Bang YJ, et al. HELOISE: Phase IIIb randomized multicenter study comparing standard-of-care and higher-dose trastuzumab regimens combined with chemotherapy as first-line therapy in patients with human epidermal growth factor receptor 2-positive metastatic gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol* 2017; **35:** 2558–67.

21 Hecht JR, Bang YJ, Qin SK, et al. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC—a randomized phase III trial. *J Clin Oncol* 2016; **34:** 443–51.

22 Thuss-Patience PC, Shah MA, Ohtsu A, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncol* 2017; **18:** 640–53.

23 Roche Registration Ltd. Kadcyla (trastuzumab emtansine). Annex 1. Summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002389/WC500158593.pdf (accessed Jan 9, 2018).

24 Genentech Inc. KADCYLA (ado-trastuzumab emtansine). Prescribing information (USA). http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125427lbl.pdf (accessed Jan 9, 2018).

25 GlaxoSmithKline. TYKERB (lapatinib). Prescribing information (USA). http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022059s007lbl.pdf (accessed Jan 9, 2018).

26 Novartis Europharm Limited. Tyverb (lapatinib). Annex 1. Summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000795/WC500044957.pdf (accessed Jan 9, 2018).

27 Ter Veer E, Creemers A, de Waal L, van Oijen MGH, van Laarhoven HWM. Comparing cytotoxic backbones for first-line trastuzumab-containing regimens in human epidermal growth factor receptor 2-positive advanced oesophagogastric cancer: A meta-analysis. *Int J Cancer* 2018; **143:** 438–48.