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

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Summary

Background **Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2; also known as ERBB2), was investigated in combination with chemotherapy for first-line treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer.**

Methods **ToGA (Trastuzumab for Gastric Cancer) was an open-label, international, phase 3, randomised controlled trial undertaken in 122 centres in 24 countries. Patients with gastric or gastro-oesophageal junction cancer were eligible for inclusion if their tumours showed overexpression of HER2 protein by immunohistochemistry or gene amplification by fluorescence in-situ hybridisation. Participants were randomly assigned in a 1:1 ratio to receive a chemotherapy regimen consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin given every 3 weeks for six cycles or chemotherapy in combination with intravenous trastuzumab. Allocation was by block randomisation stratified by Eastern Cooperative Oncology Group performance status, chemotherapy regimen, extent of disease, primary cancer site, and measurability of disease, implemented with a central interactive voice recognition system. The primary endpoint was overall survival in all randomised patients who received study medication at least once. This trial is registered with ClinicalTrials.gov, number NCT01041404.**

Findings **594 patients were randomly assigned to study treatment (trastuzumab plus chemotherapy, n=298; chemotherapy alone, n=296), of whom 584 were included in the primary analysis (n=294; n=290). Median follow-up was 18·6 months (IQR 11–25) in the trastuzumab plus chemotherapy group and 17·1 months (9–25) in the chemotherapy alone group. Median overall survival was 13·8 months (95% CI 12–16) in those assigned to trastuzumab plus chemotherapy compared with 11·1 months (10–13) in those assigned to chemotherapy alone (hazard ratio 0·74; 95% CI 0·60–0·91; p=0·0046). The most common adverse events in both groups were nausea (trastuzumab plus chemotherapy, 197 [67%] *vs* chemotherapy alone, 184 [63%]), vomiting (147 [50%] *vs* 134 [46%]), and neutropenia (157 [53%] *vs* 165 [57%]). Rates of overall grade 3 or 4 adverse events (201 [68%] *vs* 198 [68%]) and cardiac adverse events (17 [6%] *vs* 18 [6%]) did not differ between groups.**

Interpretation **Trastuzumab in combination with chemotherapy can be considered as a new standard option for patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer.**

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Introduction

Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related deaths worldwide.[1,2] Most patients present with inoperable advanced or metastatic disease requiring palliative treatment, although early detection is more common in Asia than in other regions. In the UK MAGIC study,[3] 5-year survival was 36% in patients with operable disease who were assigned to perioperative chemotherapy. However, 5-year survival for advanced or metastatic gastric cancer is around 5–20%, with median overall survival being less than 1 year.[2,4,5] A meta-analysis of phase 2 and 3 randomised gastric cancer trials has shown that combination chemotherapy results in substantially improved overall survival compared with single-agent chemotherapy or best supportive care.[6] Typically, a fluoropyrimidine and a platinum compound form the backbone of chemotherapy for patients with advanced gastric cancer. There is currently no single well established standard of care, but fluoropyrimidine-based and platinum-based combinations with or without a third drug (usually docetaxel or epirubicin) are the most widely used combinations in Europe and the USA. The oral fluoropyrimidine capecitabine was shown to be non-inferior to fluorouracil in terms of progression-free survival and overall survival in clinical trials.[7,8]

Despite the recently reported benefits of combination therapies, the prognosis of advanced gastric or gastro-oesophageal cancer remains poor, and new treatments showing acceptable toxicity profiles are urgently needed.

	Surgical specimen staining pattern	Biopsy specimen staining pattern	HER2 overexpression assessment
0	No reactivity or membranous reactivity in <10% of tumour cells	No reactivity or no membranous reactivity in any tumour cell	Negative
1+	Faint or barely perceptible membranous reactivity in ≥10% of tumour cells; cells are reactive only in part of their membrane	Tumour cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of tumour cells stained	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells	Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells	Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Positive

HER2=human epidermal growth factor receptor 2 (also known as ERBB2).

Table 1: **Immunohistochemistry scoring for HER2 in gastric and gastro-oesophageal junction cancer, by type of diagnostic specimen**

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One well established target is human epidermal growth factor receptor 2 (HER2; also known as ERBB2), a member of a family of receptors associated with tumour cell proliferation, apoptosis, adhesion, migration, and differentiation.[9] There is growing evidence that HER2 is an important biomarker and key driver of tumorigenesis in gastric cancer, with studies showing amplification or overexpression in 7–34% of tumours.[9–11] Although reports are conflicting, some studies have suggested that HER2-positive status in gastric cancer is associated with poor outcomes and aggressive disease.[9,11]

Trastuzumab, a monoclonal antibody that targets HER2, induces antibody-dependent cellular cytotoxicity, inhibits HER2-mediated signalling, and prevents cleavage of the extracellular domain of HER2.[12] In HER2-positive breast cancer, trastuzumab has shown a survival advantage in early and metastatic disease and is now the standard of care.[13–15] In patients with metastatic breast cancer, high levels of HER2-protein expression and amplification predict for better outcomes with trastuzumab.[14] However, this relation is less clear in patients with early breast cancer[16] and has not been established in other tumour types with HER2 overexpression. In preclinical models of gastric cancer, trastuzumab showed at least additive antitumour effects when combined with capecitabine or cisplatin, or both.[17] In view of the high unmet medical need in gastric cancer, a HER2 positivity rate similar to breast cancer,[18–20] and the good tolerability profile of trastuzumab in patients with breast cancer,[13,15] investigation of trastuzumab in patients with gastric cancer was warranted.

The objective of the Trastuzumab for Gastric Cancer (ToGA) study was to assess the clinical efficacy and safety of trastuzumab added to chemotherapy for first-line treatment of advanced gastric or gastro-oesophageal junction cancers with overexpression of HER2.

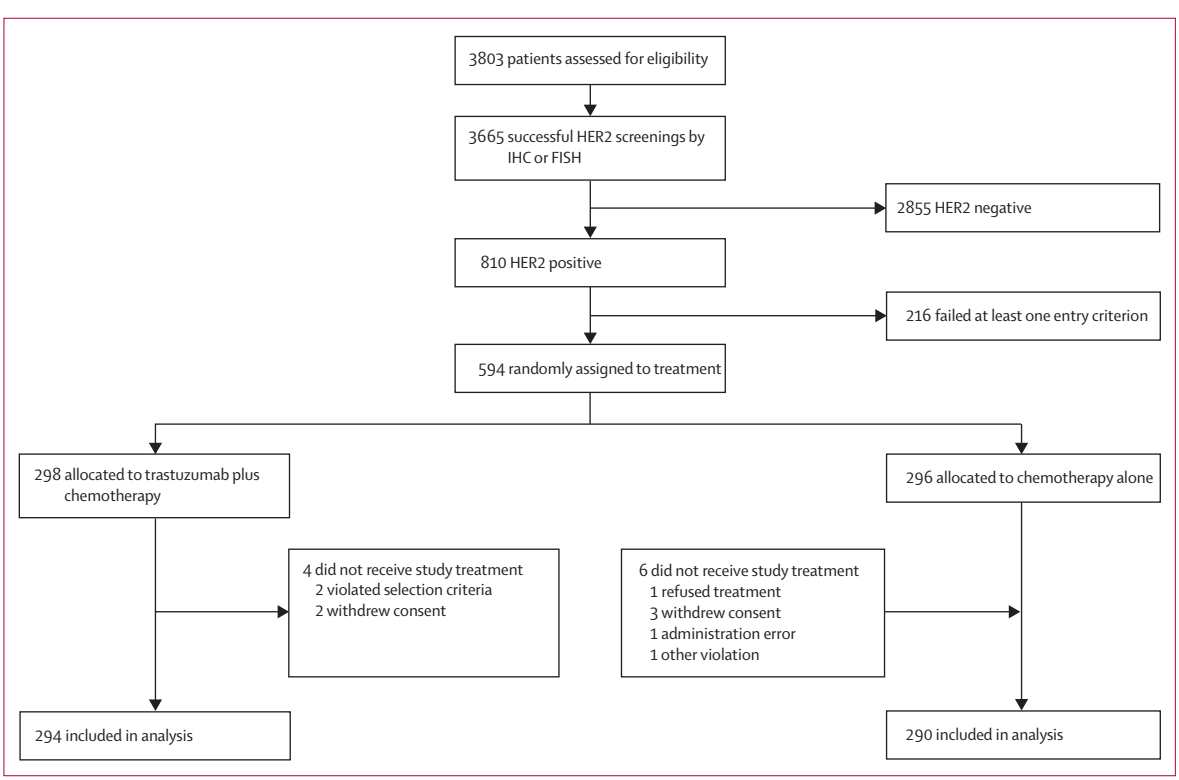

Figure 1: **Trial profile**
HER2=human epidermal growth factor receptor 2 (also known as ERBB2). IHC=immunohistochemistry. FISH=fluorescence in-situ hybridisation.

Methods

Study design and participants

ToGA was a randomised, open-label, multicentre, international, phase 3, randomised controlled trial undertaken in 24 centres in Asia, Central and South America, and Europe. Men or women older than 18 years of age were eligible for inclusion if they had histologically confirmed inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; adequate organ function; and measurable or non-measurable disease. Tumours were centrally tested for HER2 status with immunohistochemistry (HercepTest, Dako, Denmark]) and fluorescence in-situ hybridisation (FISH; HER2 FISH pharmDx, Dako). Because of the inherent biological differences between breast and gastric tumours, notably tumour heterogeneity and the occurrence of baso(lateral) membrane staining, a new set of immunohistochemistry scoring criteria were developed that are specific for gastric cancer. These scoring criteria were modified on the basis of the study by Hofmann and colleagues,[10] and are described in table 1. Patients were eligible if their tumour samples were scored as 3+ on immunohistochemistry or if they were FISH positive (HER2:CEP17 ratio ≥2).

Major exclusion criteria included previous chemotherapy for metastatic disease, congestive heart failure, baseline left ventricular ejection fraction (LVEF) less than 50%, transmural myocardial infarction, uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg), angina pectoris requiring medication, clinically significant valvular heart disease, high-risk arrhythmias, lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome, active gastrointestinal bleeding, and evidence of brain metastases.

The study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. Approvals for the study protocol (and any modifications thereof) were obtained from independent ethics committees.

Randomisation and masking

Patients who satisfied all eligibility criteria (including defined HER2 status and stratification factors) were randomly assigned in a 1:1 ratio to receive trastuzumab (Herceptin, F Hoffmann-La Roche, Basel, Switzerland) plus chemotherapy (capecitabine [Xeloda, F Hoffmann-La Roche] plus cisplatin or fluorouracil plus cisplatin, chosen at the investigator's discretion) or chemotherapy alone. Treatment was assigned by use of a randomised block design with block sizes of four patients, via a central interactive voice recognition system (by telephone). The randomisation sequence was created by F Hoffmann-La Roche and was used by the interactive voice recognition system to allocate treatment assignment. At randomisation, patients were stratified according to ECOG performance status, chemotherapy regimen, extent of disease, primary cancer site, and measurability of disease. Neither patients nor investigators were masked to treatment assignment in this open-label trial.

	Trastuzumab plus chemotherapy (n=294)	Chemotherapy alone (n=290)
Age (years)	59·4 (10·8)	58·5 (11·2)
ECOG performance status		
0–1	264 (90%)	263 (91%)
2	30 (10%)	27 (9%)
Men	226 (77%)	218 (75%)
Ethnic origin		
Black	1 (<1%)	2 (1%)
White	115 (39%)	105 (36%)
Asian	151 (51%)	158 (54%)
Other	27 (9%)	25 (9%)
Chemotherapy regimen		
Capecitabine and cisplatin	256 (87%)	255 (88%)
Fluorouracil and cisplatin	38 (13%)	35 (12%)
Primary tumour site		
Stomach	236 (80%)	242 (83%)
Gastro-oesophageal junction	58 (20%)	48 (17%)
Type of gastric cancer (assessed by central laboratory)*		
Intestinal	225 (77%)	213 (74%)
Diffuse	26 (9%)	25 (9%)
Mixed	42 (14%)	49 (17%)
Measurable tumour	269 (91%)	257 (89%)
Extent of disease at study entry		
Locally advanced	10 (3%)	10 (3%)
Metastatic	284 (97%)	280 (97%)
Metastatic sites per patient†		
1–2	152 (52%)	146 (50%)
>2	141 (48%)	144 (50%)
Previous radiotherapy	5 (2%)	7 (2%)
Previous anthracycline therapy	2 (1%)	2 (1%)
Previous chemotherapy	27 (9%)‡	12 (4%)‡
Previous gastrectomy	71 (24%)	62 (21%)
HER2 status		
FISH positive/IHC 0	23 (8%)	38 (13%)
FISH positive/IHC 1+	38 (13%)	32 (11%)
FISH positive/IHC 2+	80 (27%)	79 (27%)
FISH positive/IHC 3+	131 (45%)	125 (43%)
FISH negative/IHC 3+	9 (3%)	6 (2%)
FISH positive/IHC no result	5 (2%)	2 (1%)
FISH no result/IHC 3+	8 (3%)	8 (3%)

Data are mean (SD) or number (%). ECOG=Eastern Cooperative Oncology Group. HER2=human epidermal growth factor receptor 2 (also known as ERBB2). FISH=fluorescence in-situ hybridisation. IHC=immunohistochemistry. *Trastuzumab plus chemotherapy, n=293; chemotherapy alone, n=287. †Trastuzumab plus chemotherapy, n=293. ‡p<0·0146 for comparison between groups (χ^2 test).

Table 2: **Patient demographics and baseline characteristics**

For the **full protocol for this trial** see http://www.rochetrials.com/trialDetailsGet.action?studyNumber=BO18255&productGenericName=trastuzumab+%5BHerceptin%5D&productType=Drug&divisionName=PHA

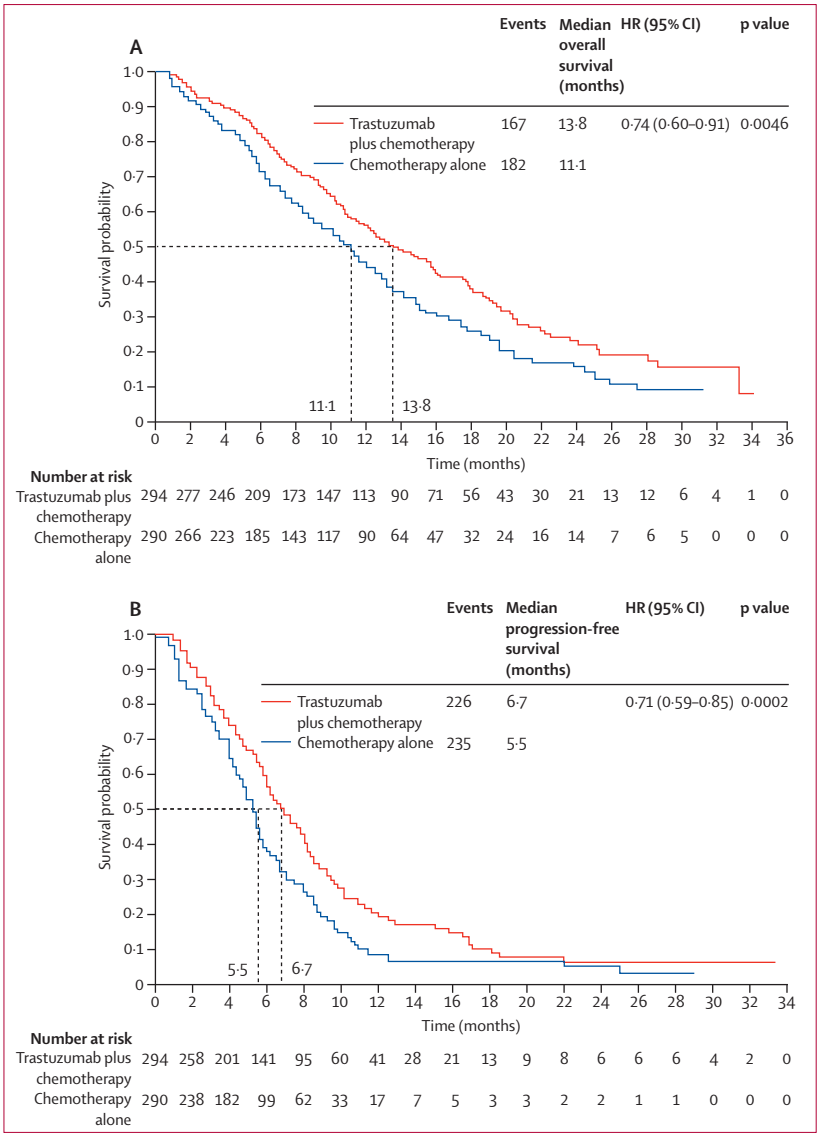

Figure 2: **(A) Median overall survival and (B) progression-free survival in the primary analysis population**
HR=hazard ratio.

Procedures

Chemotherapy was given every 3 weeks for six cycles. Capecitabine 1000 mg/m² was given orally twice a day for 14 days followed by a 1-week rest, or fluorouracil 800 mg/m² per day was given by continuous intravenous infusion on days 1–5 of each cycle. Cisplatin 80 mg/m² on day 1 was given by intravenous infusion. Trastuzumab was given by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. Chemotherapy dose adjustments were allowed. Trastuzumab toxicity was managed by treatment interruptions. Crossover to trastuzumab at the time of disease progression was not allowed.

The primary endpoint was overall survival, defined as time from randomisation until death from any cause. Secondary endpoints included progression-free survival, time to progression, overall tumour response rate, duration of response, and safety. LVEF assessments were done at baseline and at least every 12 weeks. Patients were followed up until death, loss to follow-up, or end of study. Efficacy and safety data were monitored by an independent data monitoring committee. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 and serious adverse events according to International Conference on Harmonisation guidelines. Two interim efficacy analyses were planned, at 50% and 75% of events; the latter was deemed final by the independent data monitoring committee.

After the start of the trial, time to progression was added as a secondary endpoint and the safety follow-up was extended from 4 weeks to 6 months because of the long half-life of trastuzumab.

Statistical analysis

The planned sample size was 584 patients, allowing for a 10% dropout rate and assuming an improvement in overall survival from 10 months to 13 months by the addition of trastuzumab to chemotherapy, following an exponential distribution of survival. The initial median overall survival in this trial was estimated on the basis of data from previous comparative studies and HER2 postitivity being a negative prognostic factor for outcome of patients. Therefore, median overall survival in the comparator group was estimated to be 7 months. Through discussions at several advisory board meetings, an improvement of 3 months to a median of 10 months by the addition of trastuzumab was considered clinically significant. During the study, the independent data monitoring committee noted a lower than expected event rate. On the basis of a longer than projected median survival of patients treated with capecitabine and cisplatin (10·4 months) in the pivotal ML17032 trial,[8] the independent data monitoring committee recommended revision of the original assumptions. To detect an intended difference of 3 months between the two groups and taking into account that the overall survival in the control group could be as long as 10 months, the calculated hazard ratio (HR) increased from 0·7 to 0·77. If the data were to be analysed once (fixed sample study), 460 events were necessary to ensure a power of 80% for a two-sided log-rank test at an α level of 0·05 to show a significant difference in the primary endpoint.

Two efficacy interim analyses were done at approximately 50% and 75% of the total 460 targeted events; the statistical significance level was determined by applying the O'Brien-Fleming boundary with the Lan-DeMets spending function with the actual number of events at the time of the interim efficacy analysis. With approximately 75% of the information (349 events)

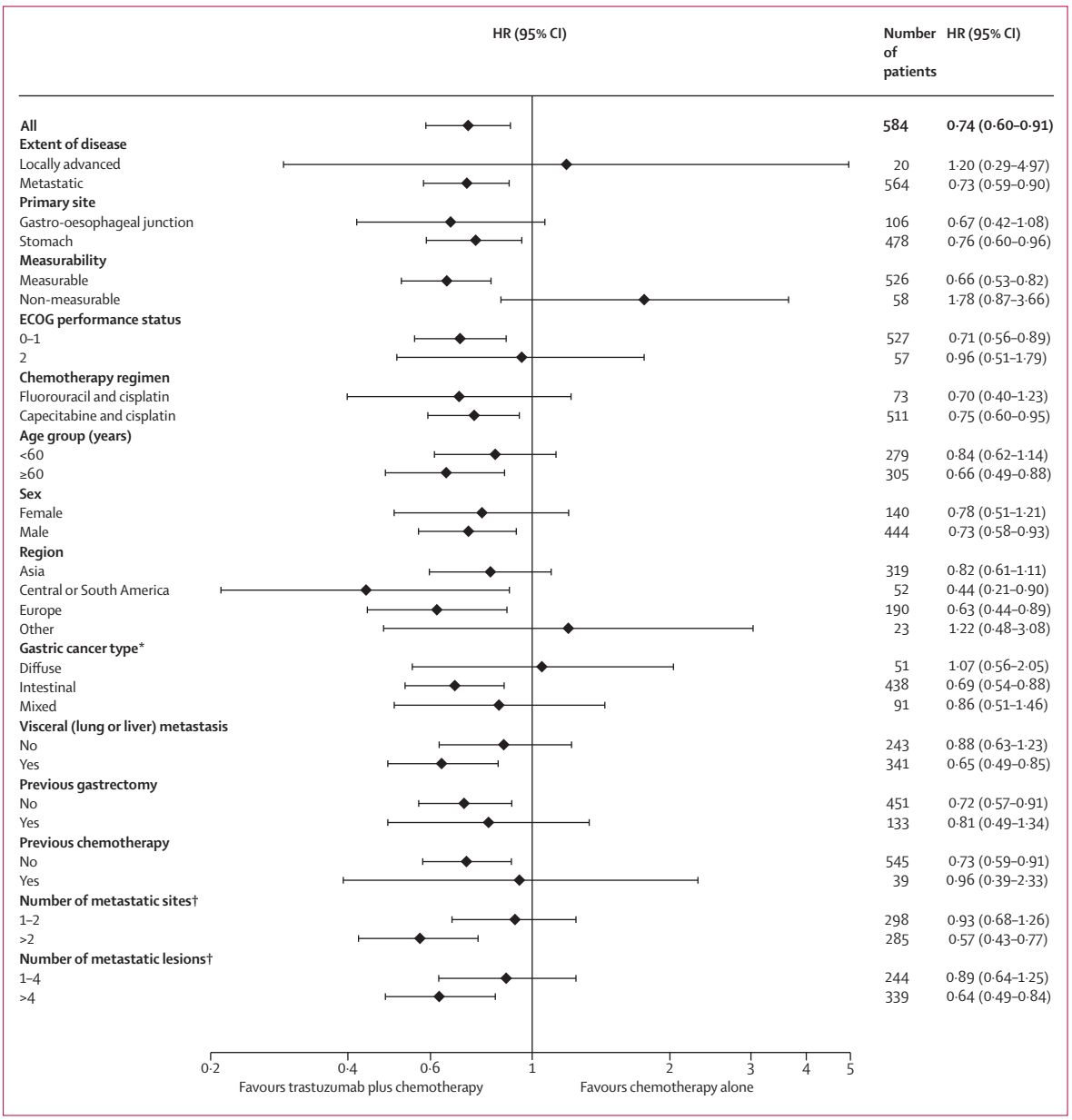

Figure 3: **Hazard ratios and 95% CIs for overall survival in prespecified subgroups**
HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group. *Four patients could not be assessed for gastric cancer type (one patient in the trastuzumab plus chemotherapy group and three patients in the chemotherapy alone group). †One patient did not receive an assessment for target and non-target lesions at baseline in the trastuzumab plus chemotherapy group.

reported, the boundary for statistical significance for overall surivival was crossed.

All randomised patients who received study medication at least once were included in the analysis of the primary endpoint. Patients without an event (death) were censored at the date that they were last known to be alive. Time-to-event endpoints were compared by use of the non-stratified log-rank test. Tumour response rates were analysed with a χ^2 test. All reported p values are two-sided. Kaplan-Meier estimates and Cox regression analyses of overall survival and progression-free survival were done. The log-rank test was used to compare the distribution between the two treatment groups. Both stratified and unstratified analyses were undertaken. Subgroup analyses were undertaken to investigate the consistency of the treatment effect for multiple baseline characteristics by use of a Cox regression model. For the subgroup analysis of overall survival, the HR and 95% CI within each subgroup were summarised and displayed in the forest plot. The log-likelihood ratio test for interactions was used to assess to heterogeneity of treatment effects for levels of baseline characteristics. All

	Trastuzumab plus chemotherapy (n=294)	Chemotherapy alone (n=290)	Non-stratified effect size		Stratified effect size*		Odds ratio	p value
			Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value		
Progression-free survival (months)	6·7 (6–8)	5·5 (5–6)	0·71 (0·59–0·85)	0·0002	0·71 (0·59–0·86)	0·0004	..	..
Time to progression (months)	7·1 (6–8)	5·6 (5–6)	0·70 (0·58–0·85)	0·0003	0·69 (0·57–0·84)	0·0003	..	..
Duration of response (months)	6·9 (6–8)†	4·8 (4–6)‡	0·54 (0·40–0·73)	<0·0001	0·53 (0·39–0·73)	<0·0001	..	..
Tumour response								
Overall tumour response rate	139 (47%)	100 (35%)	..	..	..	..	1·70 (1·22–2·38)	0·0017§
Complete response	16 (5%)	7 (2%)	..	..	..	..	2·33 (0·94–5·74)	0·0599§
Partial response	123 (42%)	93 (32%)	..		..	..	1·52 (1·09–2·14)	0·0145§
Stable disease	93 (32%)	101 (35%)	..	..	..	..	..	..
Progressive disease	35 (12%)	53 (18%)	..	..	..	..	..	..
Missing	27 (9%)	36 (12%)	..	..	..	..	..	..

Data are median (95% CI) or number (%). *Stratified by extent of disease (local *vs* metastatic), primary tumour site (stomach *vs* gastro-oesophageal junction), measurability (measurable *vs* non-measurable), Eastern Cooperative Oncology Group performance status (0–1 *vs* 2), and fluoropyrimidine regimen (fluorouracil *vs* capecitabine). †n=139. ‡n=100. §χ^2 test.

Table 3: **Secondary efficacy endpoints**

15 prespecified subgroup analyses are reported. One post-hoc subgroup analysis was done (in patients with immunohistochemistry 2+ and FISH-positive tumours or immunohistochemistry 3+ tumours) and is reported. No adjustment was made for multiple tests between treatment and baseline characteristics; since 15 were tested, one might be significant by chance. Analyses were done with SAS version 8.2.

See Online for webappendix

This study is registered with ClinicalTrials.gov, number NCT01041404 (CenterWatch study number 147440).

Role of the funding source

The sponsor of the study was involved in study design, data interpretation, and the decision to submit the report for publication in conjunction with the authors. Employees of the sponsor collected and managed the data, and undertook data analysis. The two principal investigators (Y-JB and EVC) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between September, 2005, and December, 2008, 594 patients were randomly assigned to study treatment at 122 centres in 24 countries. 584 randomised patients who received study treatment at least once were included in the analysis.

Table 2 shows demographics and baseline disease characteristics of patients included in the analysis. Most patients received a chemotherapy regimen that included capecitabine (88%). High expression of HER2 protein (ie, immunohistochemistry 2+ and FISH positive or immunohistochemistry 3+) was recorded in 446 (76%) of 584 tumours. More patients assigned to trastuzumab plus chemotherapy had received previous chemotherapy than had patients assigned to chemotherapy alone.

Median follow-up was 18·6 months (IQR 11–25) in the trastuzumab plus chemotherapy group and 17·1 months (9–25) in the chemotherapy alone group. The median number of cycles of trastuzumab therapy was eight (range 1–49). The cumulative dose of chemotherapy agents, treatment duration, and dose intensity did not differ between groups (webappendix). Second-line therapy after disease progression was given to 122 (42%) patients in the trastuzumab plus chemotherapy group (113 [38%] received chemotherapy) compared with 131 (45%) patients in the chemotherapy alone group (124 [43%] received chemotherapy; webappendix).

Median overall survival was 13·8 months (95% CI 12–16) in patients assigned to trastuzumab plus chemotherapy compared with 11·1 months (10–13) in those assigned to chemotherapy alone (HR 0·74; 95% CI 0·60–0·91; p=0·0046; figure 2), corresponding to a 26% reduction in the death rate. Consistent results were provided by a confirmatory analysis that included all 594 randomised patients (data not shown).

A treatment effect could not be excluded in any of the predefined subgroups (figure 3); the overall HR of 0·74 included the 95% CI for all subgroups, apart from the non-measurable disease subgroup. These results must be interpreted with caution because of the small numbers of events within some subgroups. Median progression-free survival was 6·7 months (95% CI 6–8) in the trastuzumab plus chemotherapy group compared with 5·5 months (5–6) in the chemotherapy alone group (HR 0·71, 95% CI 0·59–0·85; p=0·0002; figure 2 and table 3). Overall tumour response rate, time to progression, and duration of response were significantly improved in the trastuzumab plus chemotherapy group compared with the chemotherapy alone group (table 3).

A pre-planned exploratory analysis according to HER2 status suggested that overall survival was longer in patients with high expression of HER2 protein than in patients with low expression (figure 4). To further explore this finding, a post-hoc analysis divided patients into two large subgroups, with either high (immunohistochemistry 2+

and FISH positive or immunohistochemistry 3+; n=446) or low (immunohistochemistry 0 and FISH positive or immunohistochemistry 1+ and FISH positive; n=131) levels of HER2 protein in their tumours (figure 4). The HR for patients whose tumours had high HER2 expression was 0·65 (95% CI 0·51–0·83) and median overall survival was 16·0 months (95% CI 15–19) in those assigned to trastuzumab plus chemotherapy compared with 11·8 months (10–13) in those assigned to chemotherapy alone. There was evidence of a significant interaction test (p=0·036) between treatment and the two HER2 subgroups (high HER2 expression *vs* low HER2 expression).

The adverse event profile was similar between the groups, with no difference in the overall rate of adverse events (all grades or grade 3 or 4; table 4). Nausea, neutropenia, vomiting, and anorexia were the most frequently reported adverse events. Patients assigned to trastuzumab plus chemotherapy had slightly higher rates of diarrhoea, stomatitis, anaemia, thrombocytopenia, fatigue, chills, weight loss, pyrexia, mucosal inflammation, and nasopharyngitis than did patients assigned to chemotherapy alone.

There was no difference between groups in frequency of grade 3 or 4 adverse events apart from diarrhoea (table 4). Serious adverse events were reported in 95 (32%) patients in the trastuzumab plus chemotherapy group and 81 (28%) patients in the chemotherapy alone group. The proportion of patients reporting an adverse event that led to dose modifications or interruptions did not differ between groups (trastuzumab plus chemotherapy, 246 [84%] *vs* chemotherapy alone, 237 [82%]) nor did 60-day mortality (15 deaths [5%] *vs* 20 deaths [7%], respectively); treatment-related mortality was 3% (ten deaths) in the trastuzumab plus chemotherapy group versus 1% (three deaths) in the chemotherapy alone group. Severe (grade ≥3) symptoms typical of an infusion-related reaction (eg, allergic reaction or hypersensitivity, chills, arthralgia, and dyspnoea) were reported infrequently, in 17 (6%) patients in the trastuzumab plus chemotherapy group: none of these reactions were fatal.

Cardiac adverse events were rare with no difference between the trastuzumab plus chemotherapy and chemotherapy alone groups (17 [6%] *vs* 18 [6%]). Frequency of cardiac failure was low, occurring in less than 1% of patients (one patient *vs* two patients, respectively). Rates of grade 3 or 4 cardiac adverse events did not differ between groups. Four (1%) patients in the trastuzumab plus chemotherapy group had a total of five events (cardiac failure [two events in one patient], myocardial infarction, unstable angina, and myocardial ischaemia with tachycardia) compared with nine (3%) patients in the chemotherapy alone group, who had nine events (cardiac failure [two events], myocardial infarction [two events], coronary arteriospasm, atrial flutter, cardiac arrest, cardiorespiratory arrest, and Prinzmetal angina). The number of patients with cardiac dysfunction (defined as a ≥10% drop in LVEF to an absolute value <50%) was low in both treatment groups (trastuzumab plus chemotherapy, 11 [5%] of 237 *vs* chemotherapy alone, two [1%] of 187).

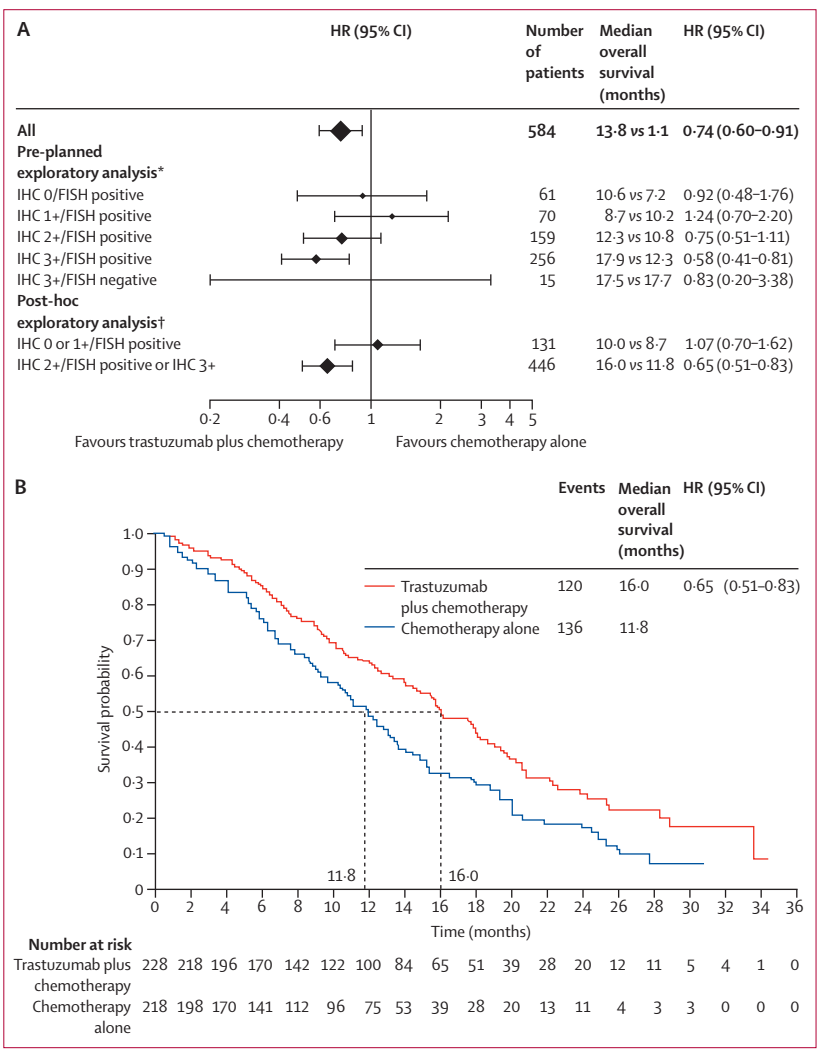

Figure 4: **Exploratory analyses**
HR=hazard ratio. (A) Pre-planned exploratory and post-hoc exploratory analyses of patients stratified by human epidermal growth factor receptor 2 (HER2) status. *n=561; patients with no immunohistochemistry (IHC) data (n=7) or IHC 3+ tumours with no fluorescence in-situ hybridisation (FISH) data (n=16) were excluded from this analysis. †n=577; patients with no IHC data (n=7) were excluded from this analysis. (B) Overall survival according to the post-hoc exploratory analysis (FISH and IHC) in patients with IHC 2+ and FISH-positive tumours or IHC 3+ tumours.

Discussion

In patients with advanced gastric or gastro-oesophageal junction cancer, addition of trastuzumab to chemotherapy significantly improved overall survival compared with chemotherapy alone. Furthermore, an exploratory, post-hoc analysis showed that trastuzumab plus chemotherapy substantially improved overall survival in patients with high expression of HER2 protein (immunohistochemistry 2+ and FISH positive or immunohistochemistry 3+) compared with patients with low expression of HER2 protein (immunohistochemistry 0 or 1+ and FISH positive).

	Trastuzumab plus chemotherapy (n=294)		Chemotherapy alone (n=290)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any adverse event	292 (99%)	201 (68%)	284 (98%)	198 (68%)
Gastrointestinal disorders				
Nausea	197 (67%)	22 (7%)	184 (63%)	21 (7%)
Vomiting	147 (50%)	18 (6%)	134 (46%)	22 (8%)
Diarrhoea	109 (37%)	27 (9%)	80 (28%)	11 (4%)
Constipation	75 (26%)	2 (1%)	93 (32%)	5 (2%)
Stomatitis	72 (24%)	2 (1%)	43 (15%)	6 (2%)
Abdominal pain	66 (22%)	7 (2%)	56 (19%)	5 (2%)
Dysphagia	19 (6%)	7 (2%)	10 (3%)	1 (<1%)
Blood and lymphatic system disorders				
Neutropenia	157 (53%)	79 (27%)	165 (57%)	88 (30%)
Anaemia	81 (28%)	36 (12%)	61 (21%)	30 (10%)
Thrombocytopenia	47 (16%)	14 (5%)	33 (11%)	8 (3%)
Febrile neutropenia	15 (5%)	15 (5%)	8 (3%)	8 (3%)
General, metabolic, and other disorders				
Anorexia	135 (46%)	19 (6%)	133 (46%)	18 (6%)
Fatigue	102 (35%)	12 (4%)	82 (28%)	7 (2%)
Hand-foot syndrome	75 (26%)	4 (1%)	64 (22%)	5 (2%)
Weight decreased	69 (23%)	6 (2%)	40 (14%)	7 (2%)
Asthenia	55 (19%)	14 (5%)	53 (18%)	10 (3%)
Pyrexia	54 (18%)	3 (1%)	36 (12%)	0
Renal impairment	47 (16%)	2 (1%)	39 (13%)	3 (1%)
Mucosal inflammation	37 (13%)	6 (2%)	18 (6%)	2 (1%)
Nasopharyngitis	37 (13%)	0	17 (6%)	0
Chills	23 (8%)	1 (<1%)	0	0
Hypokalaemia	22 (7%)	13 (4%)	13 (4%)	7 (2%)
Dehydration	18 (6%)	7 (2%)	16 (6%)	5 (2%)
Dyspnoea	9 (3%)	1 (<1%)	16 (6%)	5 (2%)

Data show adverse events of all grades (>5%) and grade 3 or 4 adverse events (≥1%) plus adverse events of any grade with more than 5% difference between groups.

Table 4: **Adverse events**

In recent years, the development of new treatments and combination chemotherapies for advanced gastric cancer has led to a steady increase in overall survival beyond the 3–5 months seen with best supportive care alone.[21,22] Single-agent chemotherapies provided an incremental benefit,[23] but the biggest advances have been seen with two-drug and three-drug combinations, as demonstrated by a meta-analysis showing a 17% reduction in the risk of death with combination regimens (HR 0·83, 95% CI 0·74–0·93).[6]

Van Cutsem and colleagues[24] reported a median overall survival of 9·2 months in patients with advanced gastric cancer who received combination therapy consisting of docetaxel, cisplatin, and fluorouracil, but this finding was associated with fairly high rates of grade 3 or 4 neutropenia, possibly because of the inclusion of a taxane. Recent trials of capecitabine plus cisplatin and of fluorouracil, leucovorin (rINN calcium folinate), and oxaliplatin have resulted in median overall survival of 10·5 months and 10·7 months, respectively.[8,25] A meta-analysis of two randomised trials, including 1318 patients, showed that capecitabine was non-inferior to fluorouracil in terms of progression-free survival and overall survival in patients with advanced gastric cancer.[26] The addition of an anthracycline to a regimen containing fluorouracil or cisplatin has also been shown to improve overall survival,[27] but before this study, the most promising results had been seen in the randomised, phase 3 REAL-2 (Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2) trial.[7] REAL-2 assessed four different three-drug combination regimens for advanced gastric cancer, and showed median overall survival of 9·9 months with epirubicin, cisplatin, and fluorouracil, 9·9 months with epirubicin, cisplatin, and capecitabine, 9·3 months with epirubicin, oxaliplatin, and fluorouracil, and 11·2 months with epirubicin, oxaliplatin, and capecitabine.[7] In this context, the current median overall survival of 13·8 months in the trastuzumab plus chemotherapy group in all patients with HER2 overexpression or amplification, and 16·0 months in patients with immunohistochemistry 2+ and FISH-positive tumours or immunohistochemistry 3+ tumours represents a clinically significant improvement.

The median overall survival of 11·1 months seen in patients assigned to chemotherapy alone was longer than expected but was in line with other studies of capecitabine-containing regimens in this population of patients.[7,8] One possible explanation is the increased use of second-line therapy in this study compared with other phase 3 studies of combination therapies.[7] Another possible explanation is that HER2 overexpression might already be conferring a better prognosis across both groups of this population of patients. However, HER2 expression leading to a better prognosis is by contrast with recent studies that showed an association between HER2-positive tumours and poor outcomes and aggressive disease;[9,11] further studies are needed to address the issue of whether HER2 has an effect on prognosis in gastric cancer, and whether it confers a good or poor prognosis. A third explanation might have been the higher percentage of patients in the control group of this study who had intestinal-type tumours compared with other phase 3 studies.[24] HER2 expression is more common in intestinal-type tumours[11] and such patients have a better outcome than do those with diffuse-type tumours,[28–30] an effect that might have led to the fairly high overall survival seen in the control group. A significant difference in progression-free survival was seen between treatment groups, but it is worth noting that progression-free survival in both groups in this trial was not substantially longer than that in other phase 3 studies of chemotherapy regimens consisting of three drugs.[7,24]

A potential weakness of this trial was the open-label nature of treatment; however, the study design was deemed acceptable for ethical reasons in seriously ill patients such as these and of low impact on the primary

endpoint of overall survival. Additionally, an independent response review was not done, which might have increased the robustness of the analyses of response rate and progression-free survival, but again this would have had no effect on the primary endpoint, overall survival. Another potential weakness is that the study was not stratified according to patients' region of origin, since other stratification factors were deemed more clinically relevant at the time of study design. At the time this study was initiated, the best possible HER2 testing modality for gastric cancer samples had not been established and the immunohistochemistry scoring criteria proposed by Hofmann and colleagues[10] were further refined during the centralised testing used in the screening phase (table 1).

In metastatic breast cancer, levels of HER2-protein expression predict the response to trastuzumab,[31] and the pre-planned analyses of overall survival according to HER2 expression in this study suggest that this association might occur in gastric cancer. On the basis of these findings, a detailed exploratory, post-hoc analysis of overall survival by subgroups defined by level of HER2-protein expression supported increased efficacy (median overall survival 16·0 months) of trastuzumab associated with high expression of the protein. Therefore, patients with advanced gastric or gastro-oesophageal junction cancer with these tumour characteristics should be offered trastuzumab plus chemotherapy as a treatment option.

The addition of trastuzumab to chemotherapy did not increase toxic effects associated with standard fluoropyrimidine-based and platinum-based chemotherapy. The most common grade 3 and 4 adverse events reported with trastuzumab plus chemotherapy were neutropenia, diarrhoea, and nausea—which occurred at similar rates to those previously described with three-drug combinations containing capecitabine or fluorouracil[7]—and anaemia. The fairly high rates of grade 3 or 4 neutropenia, stomatitis, diarrhoea, and lethargy previously reported in patients treated with the combination of docetaxel, cisplatin, and fluorouracil[24] were not seen with trastuzumab plus chemotherapy. These data show that trastuzumab can be combined with standard chemotherapy without affecting the overall safety profile. Additionally, rates of cardiac adverse events were low in this trial in patients with advanced gastric cancer (including low rates of cardiac failure and decreases in LVEF). The negligible number of patients previously exposed to anthracyclines, which are known to be toxic to myocytes,[32] might have affected these results. Few severe infusion-related reactions were reported in either group.

Thus, addition of trastuzumab to chemotherapy improved survival in patients with advanced gastric or gastro-oesophageal junction cancer compared with chemotherapy alone; this improvement was mainly the result of the survival advantage conferred to patients with high expression of HER2 protein. On the basis of these findings, trastuzumab can be considered as a new standard option for patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer when combined with a chemotherapy regimen consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin.

Contributors

All authors had full access to the original data, reviewed the data analyses, contributed to data interpretation and to the writing of the report, made final decisions on all parts of the report, and approved the final version of the submitted report. EVC, AO, Y-KK, Y-JB, and AF participated in study design. Y-JB, EVC, HCC, LS, AS, FL, AO, YO, TS, GA, EK, and Y-KK enrolled patients. JH undertook statistical analysis. JR undertook HER2 screening. AF and ML contributed to data collation and generation of tables and figures. The academic authors vouch for the completeness and veracity of the data and data analyses.

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Conflicts of interest

Y-JB and JR are advisory board members and Y-JB, EVC, FL, and Y-KK are consultants for F Hoffmann-La Roche. TS is a consultant for Chugai-Roche, Chugai Pharmaceutical, Merck-Serono, Sanofi-Aventis, Bristol-Myers, Yakult Pharmaceutical, Taiho Pharmaceutical, and Daiichi–Sankyo. Y-JB, EVC, FL, JR and Y-KK have received honoraria and Y-JB, EVC, HCC, LS, FL, AO, and GA or their institutions have received grants from F Hoffmann-La Roche. FL, GA, and JR have given educational presentations and Y-JB, JR, and Y-KK have received travel or accommodation fees from F Hoffmann-La Roche. Travel or accommodation fees have been received by AO from Chugai-Roche, and by TS from Chugai Pharmaceutical. AF, JH, and ML are employees of F Hoffmann-La Roche. AS, YO, and EK declare that they have no conflicts of interest.

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