Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial

*Charles S Fuchs, Kohei Shitara, Maria Di Bartolomeo, Sara Lonardi, Salah-Eddin Al-Batran, Eric Van Cutsem, David H Ilson, Maria Alsina, Ian Chau, Jill Lacy, Michel Ducreux, Guillermo Ariel Mendez, Alejandro Molina Alavez, Daisuke Takahari, Wasat Mansoor, Peter C Enzinger, Vera Gorbounova, Zev A Wainberg, Susanna Hegewisch-Becker, David Ferry, Ji Lin, Roberto Carlesi, Mayukh Das, Manish A Shah, RAINFALL Study Group**

Lancet Oncol 2019; 20: 420–35

Published Online February 1, 2019 http://dx.doi.org/10.1016/S1470-2045(18)30791-5

This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on April 30, 2019

See Comment page 323

*RAINFALL Study Group principal investigators listed in the appendix

Yale Cancer Center, Smilow Cancer Hospital, New Haven, CT, USA (C S Fuchs MD, Prof J Lacy MD); National Cancer Center Hospital East, Kashiwa, Japan (K Shitara MD); Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy (M Di Bartolomeo MD); Istituto Oncologico Veneto-IRCCS, Padova, Italy (S Lonardi MD); Institute of Clinical Cancer Research at Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany (Prof S-E Al-Batran MD); University Hospitals Gasthuisberg, Leuven and KULeuven, Belgium (Prof E Van Cutsem MD); Memorial Sloan Kettering Cancer Center, New York, NY, USA (D H Ilson MD); Vall d'Hebron University Hospital and Institute of Oncology, Barcelona, Spain (M Alsina MD); Royal Marsden Hospital, Sutton, Surrey, United Kingdom (I Chau MD); Gustave Roussy Cancer Centre, Grand Paris, Villejuif, France (Prof M Ducreux MD); Université Paris-Saclay, France (Prof M Ducreux); Hospital Universitario Fundacion Favaloro, Buenos Aires, Argentina (G A Mendez MD);

Summary

Background VEGF and VEGF receptor 2 (VEGFR-2)-mediated signalling and angiogenesis can contribute to the pathogenesis and progression of gastric cancer. We aimed to assess whether the addition of ramucirumab, a VEGFR-2 antagonist monoclonal antibody, to first-line chemotherapy improves outcomes in patients with metastatic gastric or gastro-oesophageal junction adenocarcinoma.

Methods For this double-blind, randomised, placebo-controlled, phase 3 trial done at 126 centres in 20 countries, we recruited patients aged 18 years or older with metastatic, HER2-negative gastric or gastro-oesophageal junction adenocarcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. Eligible patients were randomly assigned (1:1) with an interactive web response system to receive cisplatin (80 mg/m², on the first day) plus capecitabine (1000 mg/m², twice daily for 14 days), every 21 days, and either ramucirumab (8 mg/kg) or placebo on days 1 and 8, every 21 days. 5-Fluorouracil (800 mg/m² intravenous infusion on days 1–5) was permitted in patients unable to take capecitabine. The primary endpoint was investigator-assessed progression-free survival, analysed by intention to treat in the first 508 patients. We did a sensitivity analysis of the primary endpoint, including a central review of CT scans. Overall survival was a key secondary endpoint. This study is registered with ClinicalTrials.gov, number NCT02314117.

Findings Between Jan 28, 2015, and Sept 16, 2016, 645 patients were randomly assigned to receive ramucirumab plus fluoropyrimidine and cisplatin (n=326) or placebo plus fluoropyrimidine and cisplatin (n=319). Investigator-assessed progression-free survival was significantly longer in the ramucirumab group than the placebo group (hazard ratio [HR] 0·753, 95% CI 0·607–0·935, p=0·0106; median progression-free survival 5·7 months [5·5–6·5] *vs* 5·4 months [4·5–5·7]). A sensitivity analysis based on central independent review of the radiological images did not corroborate the investigator-assessed difference in progression-free survival (HR 0·961, 95% CI 0·768–1·203, p=0·74). There was no difference in overall survival between groups (0·962, 0·801–1·156, p=0·6757; median overall survival 11·2 months [9·9–11·9] in the ramucirumab group vs 10·7 months [9·5–11·9] in the placebo group). The most common grade 3–4 adverse events were neutropenia (85 [26%] of 323 patients in the ramucirumab group *vs* 85 [27%] of 315 in the placebo group), anaemia (39 [12%] *vs* 44 [14%]), and hypertension (32 [10%] *vs* 5 [2%]). The incidence of any-grade serious adverse events was 160 (50%) of 323 patients in the ramucirumab group and 149 (47%) of 315 patients in the placebo group. The most common serious adverse events were vomiting (14 [4%] in the ramucirumab group *vs* 21 [7%] in the placebo group) and diarrhoea (11 [3%] *vs* 19 [6%]). There were seven deaths in each group, either during study treatment or within 30 days of discontinuing study treatment, which were the result of treatment-related adverse events. In the ramucirumab group, these adverse events were acute kidney injury, cardiac arrest, gastric haemorrhage, peritonitis, pneumothorax, septic shock, and sudden death (n=1 of each). In the placebo group, these adverse events were cerebrovascular accident (n=1), multiple organ dysfunction syndrome (n=2), pulmonary embolism (n=2), sepsis (n=1), and small intestine perforation (n=1).

Interpretation Although the primary analysis for progression-free survival was statistically significant, this outcome was not confirmed in a sensitivity analysis of progression-free survival by central independent review, and did not improve overall survival. Therefore, the addition of ramucirumab to cisplatin plus fluoropyrimidine chemotherapy is not recommended as first-line treatment for this patient population.

Funding Eli Lilly and Company.

Research in context

Evidence before this study

Clinical evidence compiled over the past several years suggests inhibition of angiogenesis via the selective targeting of the VEGF-A/VEGFR-2 pathway is efficacious for the treatment of advanced or metastatic gastric or gastro-oesophageal junction cancer. The addition of bevacizumab, a monoclonal antibody targeting VEGF-A, to first-line chemotherapy in patients with gastric or gastro-oesophageal junction adenocarcinoma improved progression-free survival in the AVAGAST trial, but it did not increase overall survival. When ramucirumab, a fully human IgG1 monoclonal antibody VEGFR2 antagonist, was used alone (REGARD trial) or in combination with paclitaxel (RAINBOW trial) for second-line treatment of advanced gastric or gastro-oesophageal junction cancer, it provided an overall and progression-free survival benefit to patients. On the basis of these results, it was logical to investigate ramucirumab in a front line-setting in which the standard of care is a combination of fluoropyrimidine and platinum with or without a third agent. Except for patients who are HER2-positive and are eligible for treatment with trastuzumab, biomarker-enriched treatment approaches remain a challenge. The Cancer Genome Atlas data, published in 2014, identified molecular subtypes that could form the basis of patient selection. However, this knowledge can only be applied to a small group of patients. Development of the RAINFALL study rationale and protocol included review of National Comprehensive Cancer Network, European Society for Medical Oncology, and Japanese Gastric Cancer Association treatment guidelines, PubMed, and abstracts of major oncology congresses from 2009 to 2014, with MeSH and full-text search terms for clinical trials of targeted therapies for "metastatic" OR "advanced" OR "recurrent" "gastric cancer/adenocarcinoma" OR "gastro-oesophageal cancer/adenocarcinoma." Only English language publications were included.

Added value of this study

The RAINFALL study shows that although ramucirumab in combination with first-line fluoropyrimidine and cisplatin resulted in significant improvement in investigator-assessed progression-free survival, the benefit was not confirmed by an independent, central review, nor did the addition of ramucirumab to first-line chemotherapy confer an improvement in overall survival. Unlike in the second-line setting, increased ramucirumab pharmacokinetic exposure did not lead to an improvement in overall survival. The combination of ramucirumab with first-line chemotherapy appeared to be well tolerated, with similar patient-reported quality of life in both treatment groups.

Implications of all the available evidence

The results of the RAINFALL trial, combined with those of previous first-line randomised trials, indicate that the addition of an anti-angiogenic monoclonal antibody to platinum plus fluoropyrimidine chemotherapy does not improve overall survival. These results suggest that the natural history of metastatic gastric or gastro-oesophageal junction adenocarcinoma might include a change in the balance between pro-angiogenic and anti-angiogenic factors in the second-line setting, or a natural selection of tumours that are more sensitive to ramucirumab. Future efforts must be directed at identifying biomarkers that can allow better patient selection. Findings from ongoing trials could help identify patients who might benefit from immune checkpoint inhibitors and provide the basis for combining them with an antiangiogenic agent, such as ramucirumab.

Center for Clinical Care and Research in Oncology, Merida, Yucatan, Mexico (A M Alavez MD); **The Cancer Institute Hospital of JFCR, Tokyo, Japan** (D Takahari MD); **The Christie NHS Foundation Trust, Manchester, UK** (W Mansoor MD); **Dana-Farber Cancer Institute, Boston, MA, USA** (P C Enzinger MD); **N N Blokhin Russian Cancer Research Center, Moscow, Russia** (V Gorbounova MD); **David Geffen School of Medicine at UCLA, Los Angeles, CA, USA** (Z A Wainberg MD); **HOPE—Practice for Oncology, Hamburg, Germany** (Prof S Hegewisch-Becker MD); **Eli Lilly and Company, New York City, NY, USA** (D Ferry MD); **Eli Lilly and Company, Indianapolis, IN, USA** (J Lin PhD, M Das MD); **Eli Lilly Italia, Florence, Italy** (R Carlesi MD); **Weill Cornell Medical College, NY, USA** (M A Shah MD); **and New York Presbyterian Hospital, New York, NY, USA** (M A Shah)

Correspondence to:
Dr Charles S Fuchs, Yale Cancer Center, Smilow Cancer Hospital, Yale School of Medicine, New Haven, CT 06510, USA
charles.fuchs@yale.edu

See Online for appendix

Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer mortality worldwide.[1,2] Platinum compounds plus fluoropyrimidines are the most common first-line treatment for patients with metastatic (stage IV) gastric or gastro-oesophageal junction cancer, with median survival ranging from 8 to 10 months for patients with HER2-negative disease.[3–6] Clearly, new, targeted systemic agents, developed with a fundamental understanding of the biology of gastric or gastro-oesophageal junction cancer, are needed to improve the outcome of patients with advanced disease.

VEGF and VEGFR-2-mediated signalling and angiogenesis seem to play an important part in gastric cancer pathogenesis. In patients with gastric cancer, tumoral VEGF concentrations have been associated with increased tumour aggressiveness and worse survival.[7–10] Preclinical evidence suggests that tumour-induced angiogenesis could be inhibited by blocking VEGF binding to VEGFR-2 with a VEGFR-2-targeted antibody.[11]

Ramucirumab is a fully human IgG1 monoclonal antibody VEGFR-2 antagonist, which prevents ligand binding and receptor-mediated pathway activation in endothelial cells.[12] In second-line gastric or gastro-oesophageal junction adenocarcinoma, ramucirumab improved overall survival when used as monotherapy and in dual therapy with paclitaxel.[13,14] In light of the limited efficacy of existing first-line therapies for HER2-negative, advanced gastric or gastro-oesophageal junction cancer, and the documented benefit of ramucirumab in second-line treatment, we designed the RAINFALL trial to assess the safety and efficacy of ramucirumab in combination with fluoropyrimidine and cisplatin as first-line treatment in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma.

Methods

Study design and participants

RAINFALL was a randomised, placebo-controlled, double-blind, phase 3 trial, done at 126 centres in

20 countries (appendix pp 16–21). Eligible patients had stage IV, histopathologically confirmed gastric or gastro-oesophageal junction adenocarcinoma with distant metastases, according to the American Joint Committee on Cancer and Union for International Cancer Control clinical staging criteria. Investigators followed their institutional protocol to finalise diagnosis, which included histology, radiology, TNM classification, tumour location, and HER2 status. Eligible patients were aged 18 years or older, had measurable or evaluable disease according to Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1), had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, had an estimated life expectancy of 12 weeks or more in the judgment of the investigator, and had adequate organ function (as assessed by hepatic, renal, haematological, and coagulation parameters; appendix p 22). Patients were excluded if they had oesophageal cancer, had received any previous first-line systemic treatment, or had tumours that were HER2-positive. Other exclusion criteria included grade 3 or worse gastrointestinal bleeding within 3 months of randomisation (as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.0), any arterial thromboembolic event within 6 months of randomisation, or uncontrolled hypertension despite antihypertensive intervention. The complete study protocol, including a list of all eligibility criteria is included in the appendix (p 22). All institutional ethics review boards approved the study, which adhered to Good Clinical Practice guidelines and was done according to the provisions of the Declaration of Helsinki. All patients provided written, informed consent as a condition of study participation.

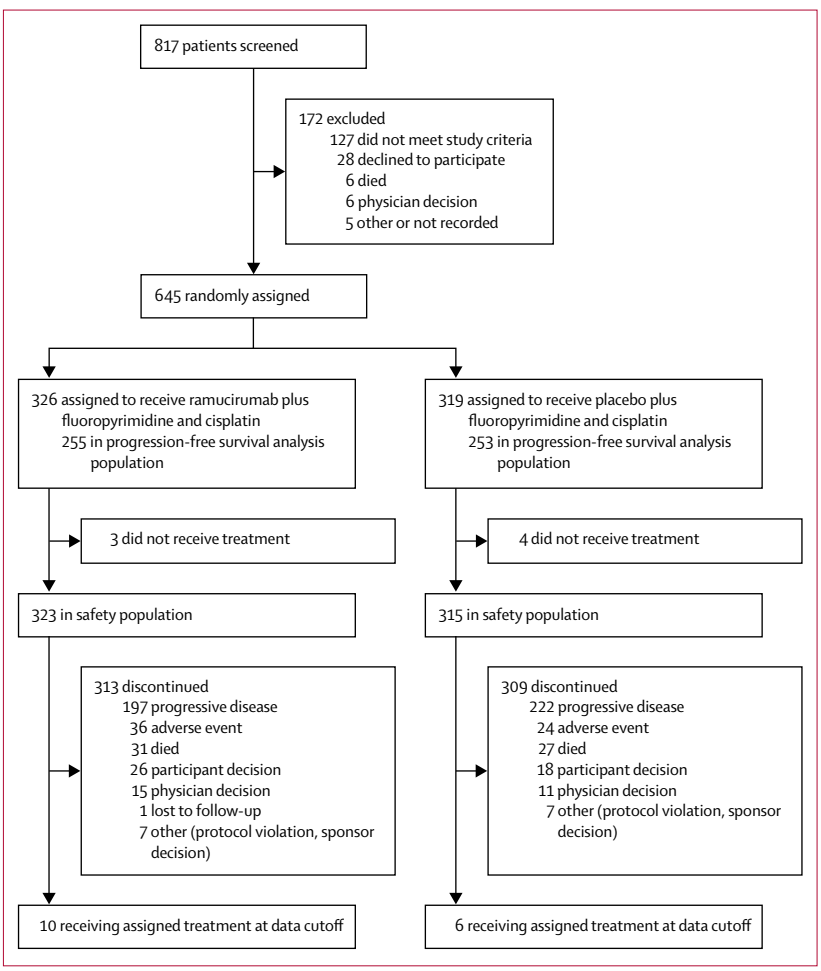


Figure 1: **Trial profile**

Randomisation and masking

Study treatment was randomly assigned (1:1) with an interactive web-response system following stratification by ECOG performance status (0 *vs* 1), primary tumour location (gastric *vs* gastro-oesophageal junction), disease measurability (measurable *vs* non-measurable), and geographic region (Japan *vs* all other countries). We generated the randomisation sequence using the block randomisation method within each stratum to maintain the balance of stratification factors. The block size was set up in the interactive web-response system and the study team was masked to block size. Patients, investigators, and study sponsor were masked to treatment assignment. Ramucirumab and placebo for infusion were identical in appearance to preserve masking. Unmasking was allowed for safety reasons, for which the identity of the study treatment was necessary for the treatment of an adverse event.

Procedures

Patients received either ramucirumab (8 mg/kg) or volume equivalent placebo intravenously on days 1 and 8 of a 21-day cycle. The dose of ramucirumab used in this trial differs from the approved dose; we chose the dose to achieve higher exposure, on the basis of modelling kinetics that supported an exposure–response relationship.[15] Both groups received cisplatin (80 mg/m² intravenously, day 1) and fluoropyrimidine (either capecitabine or 5-fluorouracil) combination chemotherapy. Capecitabine was administered orally at a dose of 1000 mg/m² twice daily, on days 1–14. Intravenous 5-fluorouracil (800 mg/m² per day, continuous infusion, days 1–5) could be substituted for oral capecitabine in patients with swallowing difficulties. The decision to treat with capecitabine or 5-fluorouracil was made before randomisation and a switch was not permitted. Patients received full supportive care as needed. Pre-defined dose modifications were allowed to manage clinically significant toxicities related to individual agents as specified in the protocol (appendix p 22). Up to two dose reductions were allowed for ramucirumab, cisplatin, and 5-fluoropyrimidine, depending on the adverse event that led to the reduction. No dose escalation was allowed after dose reduction. Up to three dose reductions were allowed

for capecitabine. Re-escalation was allowed at the discretion of the investigator after the first dose reduction. Patients received ramucirumab or placebo, and fluoropyrimidine, until radiographic or symptomatic progression, unacceptable toxicity, death, or withdrawal from the study. Symptomatic progression was defined by the trial physicians on the basis of clinical factors, for example, deterioration in performance status or increase in disease-related clinical features in the absence of objective progression in a radiological scan. At the discretion of the investigator, fluoropyrimidine could be discontinued after 1 year. Cisplatin was administered for up to 6 cycles in the absence of disease progression or other withdrawal criteria. Upon disease progression, investigators could select any second-line treatment option, including ramucirumab; however, masking for randomised treatment assignment was maintained until final overall survival data lock on Nov 6, 2017.

Study investigators did tumour assessments at baseline and every 6 weeks thereafter, from randomisation until investigator-assessed radiological progression. After discontinuation of study treatment, patient survival was assessed every 9 weeks. Local laboratory tests were done at baseline, on day 1 of each cycle, and 30 days after study treatment discontinuation. Haematology assessment was also done on day 8 of the first two cycles. Adverse events were assessed on an ongoing basis and graded with NCI-CTCAE version 4.0. Patients completed the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire[16] (EORTC QLQ-C30) at baseline, before each cycle, and at 30-day follow-up. Plasma samples for biomarker assays were collected before the ramucirumab dose on day 1 of cycle 1. An independent data monitoring committee reviewed safety and efficacy data at scheduled intervals. Biomarker assays were exploratory, individual, proprietary dual monoclonal sandwich immunoassays (version 1 for each) with antibodies internally produced at Eli Lilly and Company (Indianapolis, IN, USA). Samples for determination of ramucirumab serum trough concentration were scheduled before ramucirumab dose on day 1 of cycles 2, 3, 5, and 9, and on day 8 of cycle 1. Ramucirumab serum peak concentration samples were scheduled 1 h after the end of infusion on day 1 of cycles 1, 3, and 9. Serum concentrations of ramucirumab were analysed using a validated enzyme-linked immunosorbent assay (ELISA) method at Intertek Pharmaceutical Services (San Diego, CA, USA) or Charles River Laboratories (Senneville, QC, Canada).

Outcomes

The primary endpoint was progression-free survival, defined as the time from randomisation until the date of investigator-assessed progressive disease as described by RECIST (version 1.1), or death from any cause, whichever date was first. Overall survival was a secondary endpoint, defined as time from randomisation to death from any cause. Safety was another secondary endpoint. Other secondary endpoints included progression-free survival measured from randomisation to progression (or death) on second-line systemic therapy (PFS2), time to progression, proportion of patients achieving objective response, proportion of patients achieving disease control, and duration of response, all assessed in the overall survival intention-to-treat population. Pharmacokinetics, and quality of life were additional secondary endpoints.

	Ramucirumab plus fluoropyrimidine and cisplatin group (n=326)	Placebo plus fluoropyrimidine and cisplatin group (n=319)
Median age, years	60 (51–68)	62 (54–68)
Sex		
Male	214 (66%)	215 (67%)
Female	112 (34%)	104 (33%)
Race*		
White	256 (79%)	264 (83%)
Asian	38 (12%)	31 (10%)
Black or African American	2 (1%)	3 (1%)
Other	13 (4%)	11 (3%)
Data missing	17 (5%)	10 (3%)
ECOG performance status		
0	141 (43%)	143 (45%)
1	185 (57%)	176 (55%)
Geographic region		
North America	52 (16%)	37 (12%)
Europe	194 (60%)	205 (64%)
Japan	32 (10%)	28 (9%)
Other	48 (15%)	49 (15%)
Location of primary tumour		
Gastric	242 (74%)	239 (75%)
Gastro-oesophageal junction	83 (25%)	80 (25%)
Data missing	1 (<1%)	0
Pathological subtype		
Diffuse	141 (43%)	130 (41%)
Intestinal	108 (33%)	95 (30%)
Mixed or unknown	75 (23%)	91 (29%)
Data missing	2 (1%)	3 (1%)
Primary tumour present	263 (81%)	263 (82%)
HER2 status		
Negative	322 (99%)	312 (98%)
Not done	2 (1%)	2 (1%)
Unknown	2 (1%)	5 (2%)
Number of metastatic sites		
0–2	243 (75%)	242 (76%)
≥3	81 (25%)	76 (24%)
Data missing	2 (1%)	1 (<1%)

(Table 1 continues on next page)

	Ramucirumab plus fluoropyrimidine and cisplatin group (n=326)	Placebo plus fluoropyrimidine and cisplatin group (n=319)
(Continued from previous page)		
Peritoneal metastases		
Yes	130 (40%)	111 (35%)
No	194 (60%)	207 (65%)
Missing	2 (1%)	1 (<1%)
Measurable disease	268 (82%)	258 (81%)
Weight loss in previous 3 months*		
≥10%	88 (27%)	110 (34%)
<10%	233 (71%)	207 (65%)
Missing	5 (2%)	2 (1%)
Median duration of disease, weeks	7·1 (4–15)	6·7 (4–13)
Previous adjuvant or neoadjuvant therapy†	39 (12%)	38 (12%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. *Self-reported. †A summary of adjuvant and neoadjuvant therapy can be found in the appendix (p 6).

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

Statistical analysis

We planned enrolment to address the progression-free survival and overall survival endpoints. Enrolment of the first 508 patients, with 346 progression events, was planned to achieve 90% power to detect a difference in investigator-assessed progression-free survival between the two treatment groups (hazard ratio [HR] of 0·70, assuming an increase in median progression-free survival from 5·6 months to 8·0 months), with a two-sided α-level of 0·05. Target enrolment was 616 patients, with 467 events, to achieve 80% power to detect an overall survival difference between the two treatment groups (HR 0·77, assuming an increase in median overall survival from 10 months to 13 months), with a two-sided α-level of 0·05. The analysis of overall survival was gated, conditional on achieving statistical significance for investigator-assessed progression-free survival, to control overall type 1 error at 0·05 or less.

Progression-free survival was analysed with data from the first 508 randomly assigned patients. Overall survival was measured in all randomly assigned patients. Safety was assessed in all randomly assigned patients who received at least one dose, including a partial dose, of any study treatment (safety population). The central review population included all patients in the progression-free survival intention-to-treat population who had available radiological scans for central review.

We used a stratified log-rank test with randomisation strata (and patient data obtained via the interactive web response system) to analyse progression-free survival and overall survival data. We used the Kaplan-Meier method to estimate progression-free survival, overall survival, PFS2, time to progression, and duration of response, with medians and 95% CI and survival at various timepoints for each treatment group. We estimated HRs using a stratified Cox regression model.

We did sensitivity analyses of the primary endpoint, including a central review of radiological data (CT scans) that had been used for determination of investigator-assessed progression-free survival. For a prespecified sensitivity analysis of progression-free survival and overall survival, we constructed a multivariable Cox proportional hazards model by selecting potential confounding covariates using a stepwise selection method. The prespecified covariates were stratification factors, sex (male *vs* female), age (<65 years versus ≥65 years), race (white *vs* Asian *vs* all others), histological subtype (diffuse *vs* intestinal *vs* mixed or unknown), peritoneal metastases (yes *vs* no), weight loss (≥10% during the 3 months before study entry *vs* <10%), number of metastatic sites (≤2 versus ≥3), liver metastasis (yes *vs* no), chemo-backbone (capecitabine *vs* 5-fluorouracil), and primary tumour present (yes *vs* no). We estimated the adjusted HR for treatment effect and corresponding 95% CI from the final model after adjustment of selected confounding covariates. We compared the proportion of patients achieving an objective response and the proportion of patients achieving disease control between treatment groups using the Cochran-Mantel-Haenzel test, adjusting for randomisation strata. We analysed the HR for time to sustained deterioration in quality of life using an unstratified Cox regression model.

To understand whether possible imbalances in post-discontinuation treatment were confounding the comparison of primary therapies, we did post-hoc exploratory analyses, including assessing overall survival from randomisation or from the start of second-line treatment (referred to as landmark overall survival) for subgroups defined by whether post-discontinuation therapy was administered versus not administered, ramucirumab-containing versus all non-ramucirumab-containing therapies, and ramucirumab plus paclitaxel versus paclitaxel.

We also examined the association between ramucirumab exposure and overall survival using a post-hoc, exploratory, case-matched control analysis.[17] We used trough ramucirumab concentrations before cycle 2, day 1, for this analysis.

We analysed the predictive effect of each biomarker on progression-free survival and overall survival in a prespecified exploratory analysis using Cox's proportional hazards model with the following covariates: treatment groups, biomarker (high vs low), treatment-by-biomarker interaction, and the randomisation stratification variables. We report the HR, its two-sided 95% CI, and p value of testing the interaction of treatment and biomarkers. We investigated the association of biomarker VEGF-A with progression-free survival and overall survival in more depth using Subpopulation Treatment Effect Pattern Plot analysis, a graphical approach that

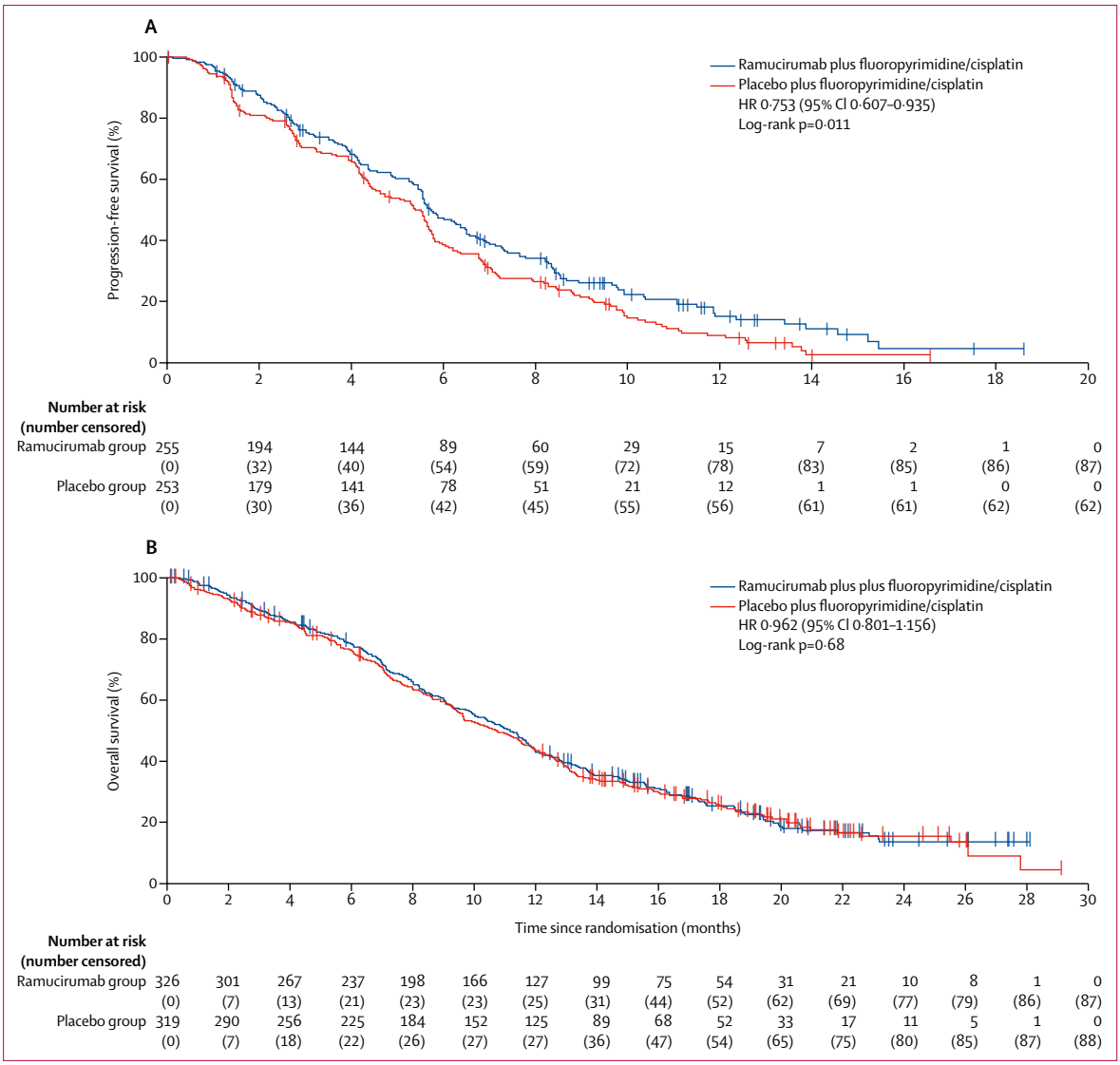


***Figure 2*: Kaplan-Meier estimates of (A) investigator-assessed progression-free survival and (B) overall survival**
HR=hazard ratio.

constructs overlapping patient subpopulations with varying values of a characteristic, in this instance VEGF-A. For this analysis, each subgroup contained at least 120 patients and overlapped with the previous subgroup by 80 or fewer patients. We determined the HR of treatment effect within each subgroup and plotted this to illustrate how treatment effect changes across VEGF-A concentrations. This trial was not powered for biomarker analyses. We made no adjustments for multiplicity.

Finally, we did post-hoc descriptive analyses to evaluate ramucirumab serum concentration in patients with and without gastrointestinal perforation.

We did all analyses using SAS (version 9.1.2 or higher). This study is registered with ClinicalTrials.gov, number NCT02314117.

Role of the funding source

The study sponsor, working with academic investigators, had a role in study and protocol design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Between Jan 28, 2015, and Sept 16, 2016, 817 patients were screened, and 645 were randomly assigned to receive either ramucirumab plus fluoropyrimidine and cisplatin (n=326) or placebo plus fluoropyrimidine and cisplatin (n=319; figure 1). The primary progression-free survival analysis, which was investigator-assessed, was done with data obtained from the first 508 randomly

	Ramucirumab plus fluoropyrimidine and cisplatin group	Placebo plus fluoropyrimidine and cisplatin group	Hazard ratio (95% CI); p value*
Investigator-assessed progression-free survival			
n (events)/N (population) (%)	168/255 (65·9%)	191/253 (75·5%)	..
Median progression-free survival, months (95% CI)	5·7 (5·5–6·5)	5·4 (4·5–5·7)	0·753 (0·607–0·935); 0·011
Overall survival			
n (events)/N (population) (%)	239/326 (73·3%)	231/319 (72·4%)	..
Median overall survival, months (95% CI)	11·2 (9·9–11·9)	10·7 (9·5–11·9)	0·962 (0·801–1·156); 0·68
Time to progression			
n (events)/N (population) (%)	177/326 (54·3%)	208/319 (65·2%)	..
Median time to progression, months (95% CI)	6·8 (5·9–7·7)	5·8 (5·6–6·4)	0·699 (0·569–0·859); 0·0006
Progression-free survival 2			
n (events)/N (population) (%)	252/326 (77·3%)	245/319 (76·8%)	..
Median progression-free survival 2, months (95% CI)	10·2 (9·0–10·8)	9·2 (8·3–10·0)	0·926 (0·774–1·108); 0·40
Best overall response by investigator review†			
Complete response	4/326 (1·2%)	5/319 (1·6%)	..
Partial response	130/326 (39·9%)	111/319 (34·8%)	..
Stable disease	133/326 (40·8%)	128/319 (40·1%)	..
Progressive disease	23/326 (7·1%)	38/319 (11·9%)	..
Non-evaluable	36/326 (11·0%)	37/319 (11·6%)	..
Overall response‡ (95% CI)	41·1% (35·8–46·4)	36·4% (31·1–41·6)	p=0·17
Disease control§ (95% CI)	81·9% (77·7–86·1)	76·5% (71·8–81·1)	p=0·095
Duration of response by investigator assessment			
Events¶	111/134 (82·8%)	106/116 (91·4%)	..
Median duration of response, months (95% CI)	5·7 (5·1–6·3)	4·3 (3·9–4·9)	0·657 (0·499–0·866); 0·0026

All efficacy measures were assessed in the intention-to-treat population (n=645), except investigator-assessed progression-free survival, which was assessed in the first 508 patients. *Two-sided log-rank p value and hazard ratio, stratified by data collected by the interactive web response system: Eastern Cooperative Oncology Group performance status, primary tumour location, disease measurability, and geographic region. †Data are n (responders)/N (population) (%), as appropriate. ‡Defined as complete response plus partial response. §Defined as complete response, partial response, plus stable disease. ¶Number of patients who progressed or died without progression/number of patients with a tumour response in the intention-to-treat population.

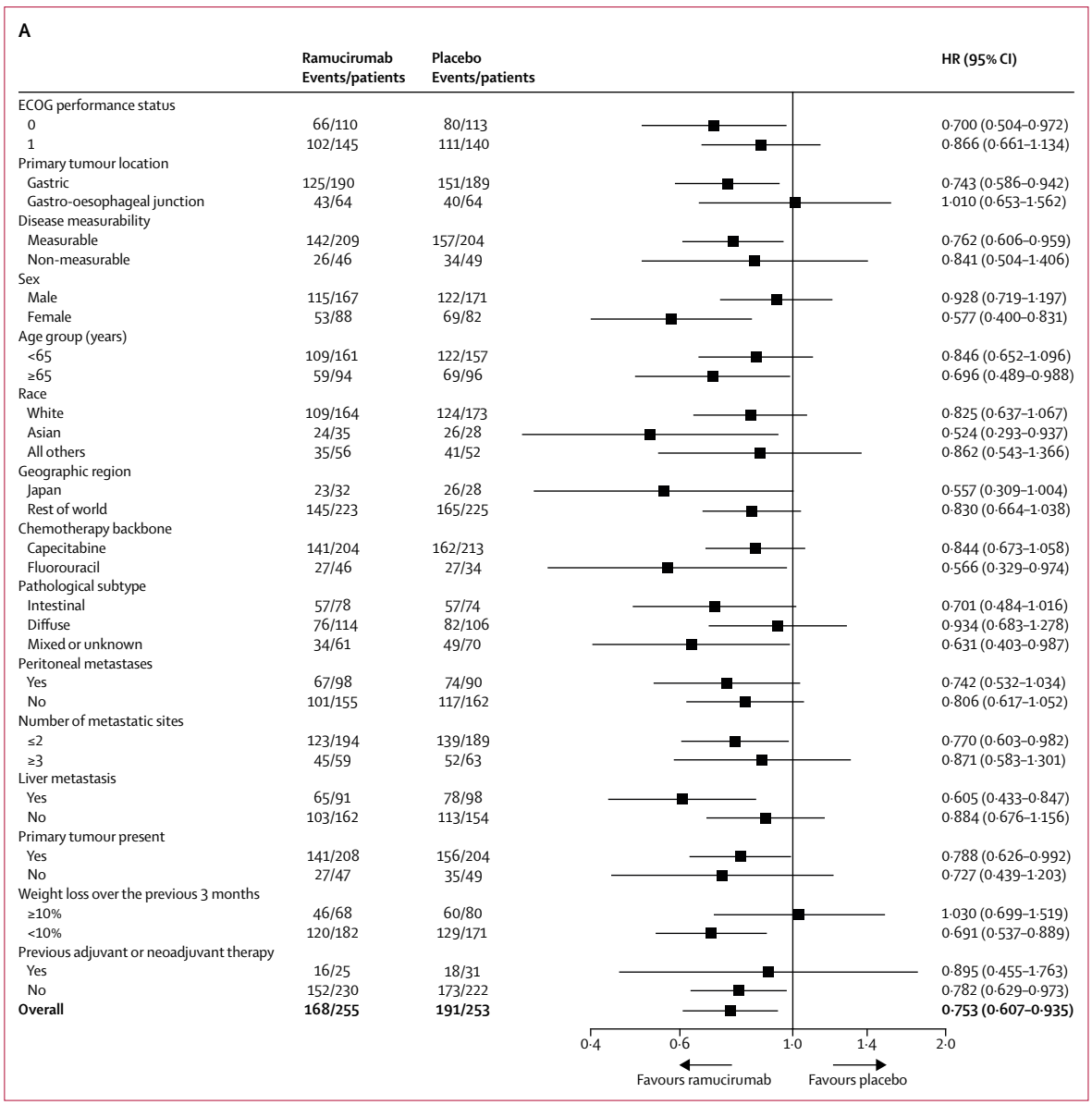
Table 2: **Efficacy outcomes**

assigned patients by the cutoff on Jan 17, 2017, when 359 progression-free survival events had been observed in these patients (n=255 in ramucirumab plus fluoropyrimidine and cisplatin group, n=253 placebo plus fluoropyrimidine and cisplatin group; the progression-free survival intention-to-treat population). We did the final overall survival analysis using data from the Nov 6, 2017, cutoff date, when 470 overall survival events were observed from the 645 randomly assigned patients (the overall survival intention-to-treat population). Baseline patient and tumour characteristics were generally well balanced between the groups (table 1; appendix p 6). For both treatment groups, disease progression was the most common reason for treatment discontinuation (figure 1).

Median treatment duration was 19·0 weeks (IQR 7·0–30·3) for ramucirumab and 18·8 weeks (7·0–29·7) for placebo (appendix p 7). Median relative dose intensity was 90·3% (IQR 81·8–99·4) for ramucirumab and 92·4% (83·9–100) for placebo. In the ramucirumab group, 269 (83%) of 323 patients in the safety population received capecitabine, and 269 (85%) of 315 received capecitabine in the placebo group. The remainder of patients received 5-fluorouracil (n=54 [17%] in the ramucirumab group, n=46 [15%] in the placebo group). The median relative dose intensity was similar between groups for both fluoropyrimidine and cisplatin (appendix p 7).

Patients treated with ramucirumab plus fluoropyrimidine and cisplatin had improved investigator-assessed progression-free survival compared with patients treated with placebo plus fluoropyrimidine and cisplatin, with a median progression-free survival of 5·7 months (95% CI 5·5–6·5) for the ramucirumab group versus 5·4 months (4·5–5·7) for the placebo group (stratified HR 0·753, 95% CI 0·607–0·935; log-rank p=0·011; figure 2A; table 2). The benefit of ramucirumab on progression-free survival was observed across several prespecified subgroups (figure 3A). In the prespecified sensitivity analysis, we identified peritoneal metastasis

A



(Figure 3 continues on next page)

and ECOG performance status as two confounding covariates in the multivariable Cox proportional hazards model for investigator-assessed progression-free survival. The adjusted HR for the investigator-assessed progression-free survival was 0·756 (95% CI 0·632–0·904; p=0·0022).

We did a sensitivity analysis on the basis of the prespecified independent central review of the radiological images of the primary outcome population (n=508). The independent review found no difference in progression-free survival between groups (HR 0·961, 95% CI 0·768–1·203, p=0·74), with a median progression-free survival of 5·5 months (95% CI 4·2–5·8) for ramucirumab and 5·4 months (4·4–5·7) for placebo (appendix pp 2, 8). Among the 458 (90%) of 508 patients with radiological scans available for central review (232 [91%] in the ramucirumab group and 226 [89%] in the placebo group), 117 (50%) of patients in the ramucirumab group and 97 (43%) of patients in the placebo group were identified by central review as having the same progression date as identified by the investigator, or both agreed there was no progression (appendix p 9).

Median follow-up for overall survival from randomisation was 10·2 months (IQR 5·6–15·5) in the ramucirumab group and 9·6 months (5·1–14·9) in the placebo group. Median overall survival did not differ between groups (figure 2B; table 2). There was no difference in overall survival in any of the prespecified subgroups (figure 3B).

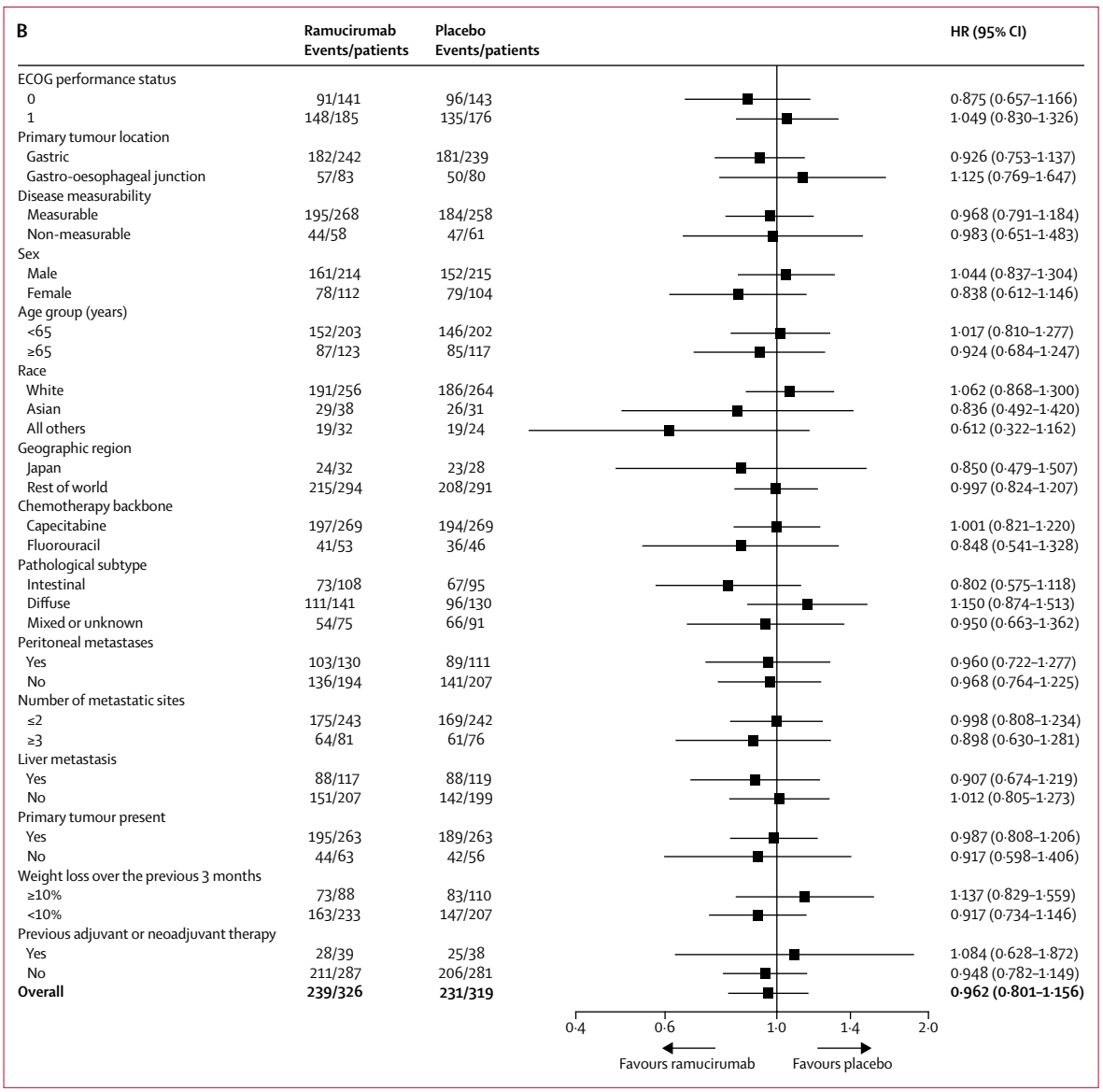


***Figure 3*: Forest plot subgroup analysis of (A) investigator-assessed progression-free survival and (B) overall survival**
Hazard ratios are based on an unstratified proportional hazards model, except for the overall stratified HR shown at the bottom of the plot. ECOG PS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio.

There was no significant difference between groups in PFS2, assessed in the intention-to-treat population (table 2; appendix p 2).

Time to progession was significantly longer in the ramucirumab group: 6·8 months (95% CI 5·9–7·7) versus 5·8 months (5·6–6·4) in the placebo group (table 2).

There was no difference in overall response with the addition of ramucirumab to fluoropyrimidine and cisplatin as compared with placebo (table 2). Likewise, disease control did not differ between groups (table 2). There was a significant difference in duration of response between groups (table 2). In a pre-specified sensitivity analysis, we selected peritoneal metastasis, ECOG performance status, geographic region, and weight loss (≥10%) over the previous 3 months as four confounding covariates in the multivariable Cox proportional hazards model for overall survival. The adjusted HR for overall survival was 0·986 (95% CI 0·821–1·184).

The most common grade 3–4 adverse events were neutropenia (85 [26%] of 323 patients in the ramucirumab group vs 85 [27%] of 315 in the placebo group), anaemia (39 [12%] *vs* 44 [14%]), and hypertension (32 [10%] *vs* five [2%]; table 3). The incidence of any-grade serious adverse events was 160 (50%) of 323 patients in the ramucirumab group and 149 (47%) of 315 patients in the

	Ramucirumab plus fluoropyrimidine and cisplatin group (n=323)				Placebo plus fluoropyrimidine and cisplatin group (n=315)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Treatment-emergent adverse events								
Neutropenia*	89 (28%)	69 (21%)	16 (5%)	0	83 (26%)	73 (23%)	12 (4%)	0
Anaemia*	71 (22%)	38 (12%)	1 (<1%)	0	73 (23%)	42 (13%)	2 (1%)	0
Hypertension	38 (12%)	32 (10%)	0	0	18 (6%)	5 (2%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	72 (22%)	28 (9%)	0	0	51 (16%)	12 (4%)	0	0
Fatigue*	165 (51%)	26 (8%)	1 (<1%)	0	159 (50%)	24 (8%)	1 (<1%)	0
Thrombocytopenia*	86 (27%)	20 (6%)	5 (2%)	0	50 (16%)	8 (3%)	3 (1%)	0
Nausea	187 (58%)	22 (7%)	0	0	161 (51%)	26 (8%)	0	0
Vomiting	121 (37%)	21 (7%)	0	0	100 (32%)	30 (10%)	1 (<1%)	0
Decreased appetite	112 (35%)	20 (6%)	1 (<1%)	0	91 (29%)	10 (3%)	0	0
Abdominal pain*	67 (21%)	17 (5%)	1 (<1%)	0	60 (19%)	11 (3%)	0	0
Leucopenia*	30 (9%)	15 (5%)	1 (<1%)	0	20 (6%)	17 (5%)	0	0
Diarrhoea	98 (30%)	14 (4%)	1 (<1%)	0	93 (30%)	19 (6%)	4 (1%)	0
Febrile neutropenia	0	11 (3%)	1 (<1%)	0	0	15 (5%)	1 (<1%)	0
Adverse events of special interest								
Hypertension	38 (12%)	32 (10%)	0	0	18 (6%)	5 (2%)	0	0
Venous thromboembolic events*	25 (8%)	15 (5%)	3 (1%)	1 (<1%)	33 (10%)	17 (5%)	3 (1%)	2 (1%)
Gastrointestinal perforation*†	1 (<1%)	7 (2%)	5 (2%)	1 (<1%)	1 (<1%)	0	0	1 (<1%)
Bleeding or haemorrhage events*	71 (22%)	7 (2%)	3 (1%)	1 (<1%)	32 (10%)	7 (2%)	4 (1%)	2 (1%)
Gastrointestinal haemorrhage events*	15 (5%)	6 (2%)	2 (1%)	1 (<1%)	6 (2%)	7 (2%)	3 (1%)	0
Proteinuria	54 (17%)	8 (2%)	0	0	31 (10%)	2 (1%)	0	0
Arterial thromboembolic events*	8 (2%)	1 (<1%)	1 (<1%)	2 (1%)	6 (2%)	5 (2%)	2 (1%)	1 (<1%)
Fistula*	0	1 (<1%)	1 (<1%)	0	0	0	0	0
Healing complication*	3 (1%)	1 (<1%)	0	0	0	0	0	0
Congestive heart failure*	0	0	0	1 (<1%)	0	0	0	0
Pulmonary haemorrhage events*	1 (<1%)	0	0	0	1 (<1%)	0	0	0

All treatment-emergent adverse events of grade 3 or worse that occur in at least 5% of patients, or that are of special interest (potentially associated with VEGF pathway inhibition or therapeutic monoclonal antibodies), regardless of cause, are listed. Events are ordered from greatest to least number of events of grade 3 or worse.
*Consolidated adverse event category comprising multiple terms. †Among the 16 patients with gastrointestinal perforation, six patients had the perforation at the primary tumour site, and another five patients had a gastric perforation without the report mentioning whether it was at the primary tumour site. Two of these five patients had the perforation at the site of an ulcer. Four patients had an intestinal perforation (small intestine or colon). The site of perforation for one patient was unknown. One of the two patients in the placebo group with a gastrointestinal perforation had a gastric perforation; the other had an intestinal perforation. One patient in the ramucirumab group had a gastric stent, which is an additional risk factor for gastric perforation.

Table 3: **Treatment-emergent adverse events in the safety population**

placebo group. There was at least a 10% higher incidence of hypertension, palmar-plantar erythrodysaesthesia syndrome, thrombocytopenia, and bleeding or haemorrhage events in the ramucirumab group than in the placebo group. Additionally, the incidence of all-grade gastrointestinal perforation was higher in the ramucirumab group (4%) than in the placebo group (1%). Most patients with gastrointestinal perforation recovered, although one patient in each group died from perforation of the small intestine or ensuing peritonitis (table 3). In post-hoc descriptive analyses, ramucirumab serum concentration among patients with gastrointestinal perforation seemed comparable with those who did not have gastrointestinal perforation (data not shown).

16 (5%) of 323 patients in the ramucirumab group and nine (3%) of 315 patients in the placebo group had an adverse event that led to reduction of study drug (appendix p 11). Adverse events that caused the discontinuation of a study drug occurred in 54 (17%) patients in the ramucirumab group and 39 (12%) patients in the placebo group (appendix p 11). The proportion of patients who had one or more serious adverse event (an event leading to hospital admission or death) was similar between treatment groups (appendix p 12). 156 (48%) patients in the ramucirumab group and 146 (46%) patients in the placebo group) were admitted to hospital because of adverse events (as counted through the study and for 30 days after treatment discontinuation), and median length of stay was

	Ramucirumab plus fluoropyrimidine and cisplatin group (n=326)	Placebo plus fluoropyrimidine and cisplatin group (n=319)
Radiotherapy	26 (8%)	18 (6%)
Surgery	20 (6%)	16 (5%)
Systemic therapy	150 (46%)	164 (51%)
Number of subsequent treatment lines		
≥1	150 (46%)	164 (51%)
≥2	52 (16%)	63 (20%)
≥3	16 (5%)	19 (6%)
4–7	3 (1%)	6 (2%)
Drugs used to treat ≥5% patients in either group		
Paclitaxel	76 (23%)	95 (30%)
Ramucirumab	40 (12%)	53 (17%)
Irinotecan	26 (8%)	42 (13%)
Fluorouracil	25 (8%)	23 (7%)
Docetaxel	19 (6%)	19 (6%)
Immune checkpoint antibody*	18 (6%)	9 (3%)
Oxaliplatin	17 (5%)	15 (5%)
Capecitabine	10 (3%)	18 (6%)

Data are n (%). *Including atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab.

Table 4: **Post-discontinuation therapy in the intention-to-treat population**

also similar (11·0 days [IQR 6–22] *vs* 11·5 days [6–20]). 18 (6%) of 323 patients in the ramucirumab group died because of an adverse event (while on therapy or within 30 days of discontinuing treatment) compared with 19 (6%) of 315 in the placebo group (appendix p 13). Among these deaths, seven in each group were considered to be related to treatment: in the ramucirumab group, these adverse events were acute kidney injury, cardiac arrest, gastric haemorrhage, peritonitis, pneumothorax, septic shock, and sudden death (n=1 of each). In the placebo group, these adverse events were cerebrovascular accident (n=1), multiple organ dysfunction syndrome (n=2), pulmonary embolism (n=2), sepsis (n=1), and small intestine perforation (n=1; appendix p 13).

To understand the effect of systemic therapies after discontinuation of first-line therapy (ie, post-discontinuation therapy), we did post-hoc exploratory analyses to examine whether imbalances in post-discontinuation therapy (including crossover) could confound the comparison of first-line therapies for overall survival. Use of any subsequent, post-discontinuation systemic therapy was similar in both groups (table 4). The use of ramucirumab as part of post-discontinuation therapy was similar between groups (table 4). Among all patients in the trial, patients who received any post-discontinuation therapy had longer median overall survival (table 5). In the post-hoc exploratory analyses, we also examined the effect of post-discontinuation ramucirumab on overall survival in patients who received at least one post-discontinuation therapy (table 5; appendix p 3). Regardless of first-line treatment assignment, patients who received ramucirumab as post-discontinuation therapy had a median overall survival of 15·0 months (95% CI 13·0–18·5), whereas patients who did not receive ramucirumab as post-discontinuation therapy had a median overall survival of 13·1 months (12·1–14·9; table 5). Additionally, in a post-hoc exploratory analysis, we assessed landmark overall survival from the start of second-line therapy for patients who received at least one post-discontinuation therapy. Regardless of the group to which participants were randomly assigned for the first-line setting, patients who received ramucirumab plus paclitaxel as post-discontinuation therapy had longer median landmark overall survival when compared with patients receiving paclitaxel (table 5; appendix p 3).

In prespecified exploratory analyses, we assessed the relationships between circulating candidate biomarkers with efficacy outcomes (progression-free survival and overall survival). VEGF-A, VEGF-C, VEGF-D, and soluble VEGFR-1 and VEGFR-3 were measured in baseline plasma samples. Treatment with ramucirumab was associated with improved progression-free survival in patients with VEGF-A concentrations lower than the median, whereas there was no improvement in those with concentrations above the median (table 6). However, more detailed prespecified analyses, modelled across the range of VEGF-A values, showed that the association between VEGF-A concentration and outcome was not consistent across the range of marker concentrations (appendix p 4).

Ramucirumab trough and peak concentration data are summarised in the appendix (p 10). In the pharmacokinetic analysis, the ramucirumab dose schedule in the trial seemed to increase drug exposure relative to that observed in previous trials using an alternative every-2-week schedule (ramucirumab serum trough concentration geometric mean value of C_{min} at week 6 was 51·2 µg/mL for RAINFALL and 45·0 µg/mL for RAINBOW).[15] Post-hoc exploratory analysis of the relationship between ramucirumab exposure (trough concentration before cycle 2, day 1) and overall survival found no apparent association (appendix p 5).

Compliance for the QLQ-C30 was high, with more than 95% of patients completing baseline assessments and more than 85% completing the on-therapy post-baseline assessments. Baseline scores were similar between groups, with mean scores for global quality of life, fatigue, and appetite loss worse than for other quality-of-life scales.[18] There were no differences in time to sustained deterioration for any of the quality-of-life scales; the unstratified HR was 1·029 (95% CI 0·786–1·347) for global quality of life, 1·088 (0·869–1·361) for fatigue, and 0·969 (0·726–1·293) for appetite loss (appendix p 14).

Discussion

The double-blind, placebo-controlled, phase 3, RAINFALL trial investigated the addition of ramucirumab to

	Patients receiving described post-discontinuation therapy		Patients not receiving described post-discontinuation therapy		HR (95% CI); p value
	Median overall survival, months	n	Median overall survival, months	n	
Any post-discontinuation therapy	13·4 (12·8–15·2)	314	7·1 (6·5–7·8)	331	0·441 (0·363–0·536); p<0·0001*
Ramucirumab-containing post-discontinuation therapy					
First-line ramucirumab	16·2 (11·7–19·4)	40	13·2 (11·9–16·3)	110	0·796 (0·485–1·308); p=0·37*
First-line placebo	14·9 (12·6–18·9)	53	13·0 (11·4–15·0)	111	0·683 (0·426–1·094); p=0·11*
Combined treatment groups	15·0 (13·0–18·5)	93	13·1 (12·1–14·9)	221	0·805 (0·580–1·118); p=0·19*
Ramucirumab plus paclitaxel post-discontinuation therapy (landmark overall survival)†					
First-line ramucirumab	9·6 (6·0–14·6)	37	6·4 (5·3–9·1)	41	0·735 (0·428–1·263); p=0·26
First-line placebo	8·6 (5·2–10·9)	46	6·8 (4·6–9·2)	53	0·956 (0·582–1·571); p=0·86
Combined treatment groups	8·6 (6·7–10·3)	83	6·7 (5·6–8·8)	94	0·819 (0·571–1·176); p=0·28

Data are median months (95% CI) or n, unless otherwise indicated. *Stratified by factors used in the primary analysis (Eastern Cooperative Oncology Group performance status, primary tumour location, disease measurability, and geographic region; appendix p 3). †Patients who did not receive ramucirumab plus paclitaxel received paclitaxel monotherapy. Results are for landmark overall survival, which is based on adjustment of covariates; results adjusted for prognostic factors if patient received any previous neoadjuvant or adjuvant therapy, ECOG performance status at start of second-line, and time to progression from first-line (appendix p 3).

Table 5: **Effect of post-discontinuation therapy (any subsequent line) on overall survival in the intention-to-treat population**

fluoropyrimidine-cisplatin chemotherapy for first-line treatment of advanced gastric or gastro-oesophageal junction adenocarcinoma. The primary objective was to investigate improvement in investigator-assessed progression-free survival; the study was also powered to investigate overall survival as an endpoint. The choice of progression-free survival as primary efficacy variable allowed us to interpret the efficacy results without interference from additional treatments following tumour progression. Although investigator-assessed progression-free survival provided real-time assessment of disease status on the basis of clinical, laboratory, and radiological assessments, we included an independent central review of progression-free survival scans as a sensitivity analysis to ensure consistency.

Ramucirumab treatment resulted in a significant improvement in investigator-assessed progression-free survival. However, the magnitude of the difference in median progression-free survival was only 0·3 months, and therefore not clinically significant. The improved progression-free survival with ramucirumab treatment was not confirmed by a sensitivity analysis of the independent, central review of the 458 patients (90% of the 508 initial patients) for whom radiological scans were available. Moreover, the addition of ramucirumab to first-line chemotherapy did not improve overall survival, nor did we observe improved overall survival in any patient subgroup. Similarly, other efficacy parameters did not show significant improvement. On the basis of these efficacy results, ramucirumab in combination with cisplatin-fluoropyrimidine cannot be recommended for first-line treatment.

The combination of ramucirumab with first-line chemotherapy seemed to be well tolerated. Hypertension, an adverse event associated with most anti-angiogenic therapies,[19] was more common in the ramucirumab group. There were no grade 4–5 hypertension events, but grade 3 hypertension was noted in 10% of patients in the ramucirumab group (*vs* 2% of patients in the placebo group). The addition of ramucirumab to cisplatin and fluoropyrimidine neither resulted in an increase in arterial or venous thromboembolic events, nor an excess of grade 3 bleeding. There were more gastrointestinal perforations in the ramucirumab group than in the placebo group (n=14 patients [4%] *vs* n=2 patients [1%]); most patients recovered. This safety profile of ramucirumab plus cisplatin and fluoropyrimidine is largely consistent with the safety profile of ramucirumab shown by a meta-analysis of six placebo-controlled randomised trials in 4996 patients.[20]

Use of post-discontinuation therapy was relatively balanced between groups, suggesting that its use was unlikely to account for the absence of improved overall survival. We used post-hoc exploratory analyses to assess the effect of post-discontinuation therapy on overall survival. Patients who received any post-discontinuation therapy showed significant improvement in overall survival. Administration of a ramucirumab-containing post-discontinuation therapy regimen, irrespective of first-line treatment assignment, was associated with higher median overall survival, which was not statistically significant.

One of the strengths of the RAINFALL trial is that it was a double-blind, randomised, placebo-controlled trial with global enrolment. Two phase 3 trials in a second-line setting supported the investigation of ramucirumab in a first-line setting.[13,14] We incorporated results from previous trials into the study design: we excluded patients with oesophageal cancer,[21] increased the dose of ramucirumab from previous studies,[15] and used a gated

	Progression-free survival							Overall survival						
	High			Low				High			Low			
	Ramucirumab	Placebo	HR (95% CI)	Ramucirumab	Placebo	HR (95% CI)	$p_{interaction}$*	Ramucirumab	Placebo	HR (95% CI)	Ramucirumab	Placebo	HR (95% CI)	$p_{interaction}$*
VEGF-A	..	..	0·99 (0·76–1·29)	..	..	0·64 (0·49–0·84)	0·023	..	..	1·26 (0·96–1·64)	..	..	0·87 (0·66–1·14)	0·056
N	149	146	..	149	145	..	..	149	146	..	149	145	..	..
Median (months)	5·42 (2·76–8·34)	4·53 (2·66–8·18)	..	6·87 (4·21–11·86)	5·65 (2·79–8·77)	..	..	9·33 (5·75–14·88)	10·58 (5·45–19·32)	..	12·22 (7·13–19·42)	11·27 (7·06–18·53)	..	..
VEGF-C	..	..	0·82 (0·61–1·11)	..	..	0·81 (0·60–1·07)	0·92	..	..	1·15 (0·85 –1·56)	..	..	0·98 (0·73–1·32)	0·47
N	124	113	..	119	118	..	..	124	113	..	119	118	..	..
Median (months)	5·55 (2·83–8·94)	4·44 (2·56–7·92)	..	5·88 (3·94–8·54)	5·65 (2·73–8·77)	..	..	11·17 (6·08–17·31)	11·40 (6·51–19·32)	..	10·45 (6·54–19·38)	11·20 (6·01–19·45)	..	..
VEGF-D	..	..	0·72 (0·55–0·93)	..	..	0·89 (0·68–1·16)	0·27	..	..	1·15 (0·88–1·51)	..	..	0·95 (0·73–1·24)	0·34
N	160	139	..	142	156	..	..	160	139	..	142	156	..	..
Median (months)	5·91 (3·58–9·86)	5·59 (2·73–8·34)	..	5·65 (3·81–8·51)	5·29 (2·76–8·28)	..	..	10·87 (6·93–17·22)	11·40 (6·80–19·45)	..	11·17 (6·34–18·46)	11·07 (5·52–17·64)	..	..
Soluble VEGF-R1	..	..	0·72 (0·55–0·93)	..	..	0·85 (0·65–1·12)	0·36	..	..	1·00 (0·77–1·30)	..	..	1·06 (0·81–1·39)	0·76
N	157	147	..	145	148	..	..	157	147	..	145	148	..	..
Median (months)	6·01 (3·19–9·66)	4·53 (2·30–6·93)	..	5·75 (4·11–8·97)	5·78 (2·89–8·77)	..	..	9·95 (5·78–16·07)	9·66 (5·22–17·38)	..	11·60 (7·56–19·48)	12·32 (6·77–20·96)	..	..
Soluble VEGF-R3	..	..	0·78 (0·56–1·09)	..	..	0·91 (0·65–1·29)	0·52	..	..	1·10 (0·78–1·55)	..	..	1·07 (0·76–1·51)	0·92
N	100	84	..	89	94	..	..	100	84	..	89	94	..	..
Median (months)	5·59 (2·63–8·54)	4·37 (2·60–7·16)	..	5·75 (4·11–8·67)	5·75 (2·79–9·17)	..	..	8·54 (4·17–15·61)	9·13 (5·52–18·23)	..	11·76 (7·26–18·83)	11·53 (7·20–20·17)	..	..

Low concentrations defined as those less than the median biomarker concentration; high concentrations defined as those greater than or equal to median biomarker concentration. Median biomarker values were 0·375 ng/mL for VEGF-A, 57·6 pg/mL for VEGF-C, 0·132 ng/mL for VEGF-D, 0·124 ng/mL for VEGF-R1, and 117·257 ng/mL for VEGF-R3. *$p_{interaction}$ is the p value for treatment-by-marker level interaction. HR=hazard ratio.

Table 6: Efficacy outcomes by candidate biomarker subgroup, dichotomised at median concentration for each marker

statistical assessment to adequately power our analysis of progression-free survival and overall survival. There were no significant differences in outcome in our subgroup analysis by region. We identified no new safety concerns that might complicate interpretation of the results.

However, the RAINFALL trial also had some limitations. First, it is unknown whether addition of a taxane in the first-line setting could have improved outcomes. Ramucirumab has been efficacious when paired with a taxane for second-line treatment of gastric or gastro-oesophageal junction cancer (RAINBOW trial),[14] and the REGARD[13] trial showed single-agent activity. On the basis of these results, it was logical to assess ramucirumab in a front-line setting in which the standard of care is a combination of fluoropyrimidine and platinum with or without a third agent. The benefit-to-risk profile of adding a third agent, such as docetaxel or anthracycline, in a first-line setting is not fully established. Because cisplatin and fluoropyrimidine regimens are considered an acceptable standard and have been used as a backbone for other targeted agents, such as trastuzumab, the benefit-to-risk profile of this chemotherapy backbone was better established. This regimen is also approved in all major regulatory regions. Although it is plausible that adding a taxane in a front-line gastric cancer setting could have showed synergistic activity, we do not believe that the chemotherapy backbone played a part in the negative outcome of the RAINFALL trial. Ongoing trials combining ramucirumab with the FLOT regimen (fluoropyrimidine plus platinum plus taxane; NCT02661971) in a peri-operative setting might provide additional insights.

Another limitation was the unexpected absence of significance in independently-assessed progression-free survival. Although the reasons are not completely understood, this finding could be related to lack of effect of the experimental agent. Finally, the absence of a validated biomarker did not allow prospective patient selection to identify patients who might benefit the most. Exploratory analyses of circulating VEGF-family candidate biomarkers did not identify subgroups of patients who might benefit from receiving ramucirumab. To date, no biomarker has been found that reliably and consistently identifies patients most likely to benefit from antiangiogenic therapy.

Our results can be analysed in the broader context of adding an anti-angiogenic agent to chemotherapy in a first-line setting. The placebo-controlled, phase 3 AVAGAST trial[22] assessed the addition of bevacizumab, a monoclonal antibody targeting VEGF-A, to first-line chemotherapy in 774 patients with gastric or gastro-oesophageal junction adenocarcinoma. Patients treated with bevacizumab showed a significant improvement in progression-free survival (HR 0·80) but no significant improvement in overall survival. A biomarker substudy of the AVAGAST trial[23] suggested that patients with baseline high plasma VEGF-A concentration or low tumour neuropilin-1 might have benefited from bevacizumab therapy. Our data did not support better anti-angiogenic efficacy in patients with high VEGF-A concentrations, highlighting the fact that predictive biomarkers for anti-angiogenic therapies are still being sought.

In AVAGAST subset analyses, there was a progression-free survival and overall survival benefit for bevacizumab in North American and Latin American patients, a progression-free survival benefit in European patients, and no benefit in Asian patients, raising the possibility that the treatment effect for bevacizumab might differ between gastric cancers of east Asian origin versus North American and European origin.[24] In AVATAR, a 202-patient trial including only Chinese patients,[24,25] there was no improvement in progression-free survival or overall survival after the addition of of bevacizumab to capecitabine and cisplatin.[25] In our trial, the effect of ramucirumab on overall survival did not differ between Japanese patients and those from the rest of the world.

Two additional trials have also not shown a treatment benefit when ramucirumab was added to first-line gastric or gastro-oesophageal junction chemotherapy. The JVBT trial,[21] a randomised, phase 2 trial of first-line oxaliplatin plus fluoropyrimidine (FOLFOX) with or without ramucirumab for treatment of gastric or gastro-oesophageal junction and oesophageal cancer, in 180 patients, showed no improvement in progression-free survival or overall survival after treatment with ramucirumab.[21] The randomised, phase 2, RAINSTORM trial (189 patients), done in east Asia using a novel oral fluoropyrimidine derivative, S1, plus oxaliplatin as chemotherapy, also showed no improvement in efficacy when ramucirumab was added.[26] Thus, in the first-line gastric or gastro-oesophageal junction setting, 1988 patients in five randomised trials have been assessed for the benefit of adding an anti-angiogenic monoclonal antibody to platinum plus fluoropyrimidine chemotherapy, with no evidence of a survival benefit.

The natural history of metastatic gastric or gastro-oesophageal junction adenocarcinoma might include a change in the balance between pro-angiogenic and anti-angiogenic factors in the second-line setting or a natural selection of tumours more sensitive to ramucirumab. Of relevance is our finding that a higher dose of ramucirumab in this first-line chemotherapy trial did not confer a survival benefit. Additionally, there was no exposure-response effect.

Ongoing efforts to examine alternative approaches with ramucirumab might provide important information. The randomised, phase 3, ARMANI study (NCT02934464) is investigating ramucirumab plus paclitaxel as switch maintenance versus continuation of first-line chemotherapy in patients with advanced HER2-negative gastric or gastro-oesophageal junction cancer. Other clinical trials are examining the addition of ramucirumab to immune checkpoint inhibitors. The immunomodulatory action of

checkpoint inhibitors is fundamentally different to adding an anti-angiogenic to chemotherapy. The combination of ramucirumab and immune checkpoint inhibitors has produced initial clinical results for both first-line and second-line treatment.[27–30] This hypothesis-generating signal, along with a better understanding of immune manipulation that can convert an immunosuppressive tumour microenvironment to an immune-supportive one,[31] suggests that combination of antiangiogenic agents with immune checkpoint inhibitors has the potential to improve patient outcomes.

Contributors

CSF, EVC, DHI, IC, MAS, JL, MDa, and DF contributed to study concept and design. All authors contributed to the acquisition, analysis, or interpretation of the data. CSF wrote the first draft and all authors contributed to the critical review and revision of the manuscript. All authors approved the final manuscript for submission.

Declaration of interests

CSF reports a consulting role for Agios, Bain Capital, Bayer, Celgene, Dicerna, Five Prime Therapeutics, Gilead Sciences, Eli Lilly, Entrinsic Health, Genentech, KEW, Merck, Merrimack Pharmaceuticals, Pfizer, Sanofi, Taiho, Unum Therapeutics; reports serving on the Board of Directors for CytomX Therapeutics; and reports receiving unexercised stock options in CytomX Therapeutics. KS reports consulting or advisory role fees or honoraria from Astellas Pharma, Bristol-Myers Squibb, Takeda, Pfizer, Novartis, Abbvie, and Yakult; grants and personal fees from Eli Lilly and Ono Pharmaceutical; and grants from Dainippon Sumitomo Pharma, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharma, and Merck Sharpe and Dohme (MSD), all outside the submitted work. SL reports advisory role or speakers bureau fees from Amgen, Bayer, BMS, Eli Lilly, Merck, and Roche, all outside the submitted work. S-EA-B has an advisory role with Roche, Celgene, Eli Lilly, Nordic Pharma, Bristol-Myers Squibb and Merck Sharp & Dohme; is a speaker for Roche, Celgene, Eli Lilly, Nordic Pharma, AIO gGmbH, MCI, promedicis, and Forum für Medizinische Fortbildung; is CEO/Founder of IKF Klinische Krebsforschung GmbH; and has received research grants from Sanofi, Merck, Roche, Celgene, Vifor, Medac, Hospira, Eli Lilly, German Cancer Aid (Krebshilfe), German Research Foundation and the Federal Ministry of Education of Research. EVC reports grants from Amgen, Bayer, BMS, Boehringer, Celgene, Ipsen, Eli Lilly, Merck, Merck KgA, Novartis, Roche, Servier, outside the submitted work. DHI reports research trial support and advisory board fees from Eli Lilly during the conduct of the study. IC reports grants to his institution from Eli Lilly, Janssen-Cilag, Merck Serono, and Sanofi Oncology; and advisory board fees from Eli Lilly, Bristol-Myers Squibb, MSD, Roche, Five Prime Therapeutics, Astra-Zeneca, Bayer, Merck Serono, outside the submitted work; and a research grant from Eli Lilly during the conduct of the study. MDu reports advisory board or speaker fees from Merck Serono, Ipsen, Bayer, and Amgen; grants and advisory board fees from Roche, outside the submitted work; advisory board and speaker fees from Eli Lilly during the conduct of the study; and a family member who works for Sandoz. DT reports lecture fees from Eli Lilly, Taiho Pharmaceutical, Yakult, Chugai Pharmaceutical, Ono Pharmaceutical, and MSD; and grants from Taiho Pharmaceutical, all outside the submitted work. PCE reports speaker board fees from Eli Lilly, Five Prime, Merck, Astellas, Loxo, Taiho, and Celgene, all outside the submitted work. ZAW reports serving as a consultant and receiving grants from Eli Lilly, Merck, and BMS, all outside the submitted work. DF, JL, RC, and MDa are employees of Eli Lilly. MDB, MA, JL, GAM, AMA, WM, VG, SH-B, and MAS have no potential conflicts of interest to report.

Acknowledgments

We thank the patients, investigators, and institutions involved in this study. We also thank Rebecca Hozak and Sameera Wijayawardana for biomarker analysis, Ran Wei for statistical analyses, Ling Gao for pharmacokinetic work, Astra Liepa for quality-of-life analyses, Matt DiStasi for figure assistance, and Mary Dugan Wood for writing assistance. All named people were Eli Lilly employees or collaborators at the time of their involvement with the study and were compensated as such. This work was supported by Eli Lilly and Company.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65:** 87–108.
2 Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136:** E359–86.
3 Wagner AD, Syn NLX, Moehler M, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2017; **8:** CD004064. DOI:10.1002/14651858.CD004064.pub4.
4 Ajani JA, D'Amico TA, Almhanna K, et al. Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2016; **14:** 1286–312.
5 Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27:** v38–49.
6 Shen L, Shan YS, Hu HM, et al. Management of gastric cancer in Asia: resource-stratified guidelines. *Lancet Oncol* 2013; **14:** e535–47.
7 Kim SE, Shim KN, Jung SA, Yoo K, Lee JH. The clinicopathological significance of tissue levels of hypoxia-inducible factor-1α and vascular endothelial growth factor in gastric cancer. *Gut Liver* 2009; **3:** 88–94.
8 Lieto E, Ferraraccio F, Orditura M, et al. Expression of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) is an independent prognostic indicator of worse outcome in gastric cancer patients. *Ann Surg Oncol* 2008; **15:** 69–79.
9 Maeda K, Chung YS, Ogawa Y, et al. Prognostic value of vascular endothelial growth factor expression in gastric carcinoma. *Cancer* 1996; **77:** 858–63.
10 Song ZJ, Gong P, Wu YE. Relationship between the expression of iNOS, VEGF, tumor angiogenesis and gastric cancer. *World J Gastroenterol* 2002; **8:** 591–95.
11 Witte L, Hicklin DJ, Zhu Z, et al. Monoclonal antibodies targeting the VEGF receptor-2 (Flk1/KDR) as an anti-angiogenic therapeutic strategy. *Cancer Metastasis Rev* 1998; **17:** 155–61.
12 Spratlin JL, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. *J Clin Oncol* 2010; **28:** 780–87.
13 Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; **383**: 31–39.
14 Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014; **15:** 1224–35.
15 Tabenero J, Ohtsu A, Muro K, et al. Exposure-response analyses of ramucirumab from two randomized, phase III trials of second-line treatment for advanced gastric or gastroesophageal junction cancer. *Mol Cancer Ther* 2017; **16:** 2215–22.
16 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.
17 Yang J, Zhao H, Garnett C, et al. The combination of exposure-response and case-control analyses in regulatory decision making. *J Clin Pharm* 2013; **53:** 160–66.
18 Chau I, Al-Batran SE, Luft A, et al. Quality-of-life (QoL) results from RAINFALL: A randomized, double-blind, placebo (PL)-controlled phase III study of cisplatin (Cis) plus capecitabine (Cape) or 5FU with or without ramucirumab (RAM) as first-line therapy for metastatic gastric or gastroesophageal junction (G-GEJ) cancer. *Ann Oncol* 2018; published online Oct 1. DOI:10.1093/annonc/mdy282.001.
19 Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature* 2000; **407:** 249–57.
20 Arnold D, Fuchs CS, Tabernero J, et al. Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. *Ann Oncol* 2017; **28:** 2932–42.

21 Yoon HH, Bendell JC, Braiteh FS, et al. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter phase II trial. *Ann Oncol* 2016; **27:** 2196–203.

22 Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29:** 3968–76.

23 Van Cutsem E, de Haas S, Kang YK, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol* 2012; **30:** 2119–27.

24 Ohtsu A, Yoshida S, Saijo N. Disparities in gastric cancer chemotherapy between the East and West. *J Clin Oncol* 2006; **24:** 2188–96.

25 Shen L, Li J, Xu J, et al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer* 2015; **18:** 168–76.

26 Muro K, Yoshikawa T, Shitara K, et al. Randomized, double-blind, phase 2 study of S-1 plus oxaliplatin (SOX) with or without ramucirumab (RAM) as first-line therapy followed by paclitaxel plus RAM as second-line therapy in patients with advanced gastric or gastroesophageal junction adenocarcinoma (AGC). *Proc Am Soc Clin Oncol* 2018; **36**: abstr 4036.

27 Chau I, Penel N, Arkenau HT, et al. Safety and antitumor activity of ramucirumab plus pembrolizumab in treatment naive advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: Preliminary results from a multi-disease phase I study (JVDF). *Proc Am Soc Clin Oncol* 2018; **36:** abstr 101.

28 Herbst RS, Chau I, Petrylak DP, et al. Activity of ramucirumab (R) with pembrolizumab (P) by PD-L1 expression in advanced solid tumors: phase 1a/b study in later lines of therapy. *Proc Am Soc Clin Oncol* 2018; **36:** abstr 3059.

29 Takahari D, Shoji H, Hara H, et al. Preliminary result of phase 1/2 study of ramucirumab plus nivolumab in patients with previously treated advanced gastric adenocarcinoma (NivoRam study). *Proc Am Soc Clin Oncol* 2018; **36:** abstr 4047.

30 Bang Y-J, Golan T, Lin C-C, et al. Interim safety and clinical activity in patients (pts) with locally advanced and unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma from a multicohort phase I study of ramucirumab (R) plus durvalumab (D). *Proc Am Soc Clin Oncol* 2018; **36:** abstr 92.

31 Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol* 2018; **15:** 325–40.