Ramucirumab plus erlotinib in patients with untreated, *EGFR*-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Dual blockade of the EGFR and VEGF pathways in *EGFR*-mutated metastatic non-small-cell lung cancer (NSCLC) is supported by preclinical and clinical data, yet the approach is not widely implemented. RELAY assessed erlotinib, an EGFR tyrosine kinase inhibitor (TKI) standard of care, plus ramucirumab, a human IgG1 VEGFR2 antagonist, or placebo in patients with untreated *EGFR*-mutated metastatic NSCLC.

Methods This is a worldwide, double-blind, phase 3 trial done in 100 hospitals, clinics, and medical centres in 13 countries. Eligible patients were aged 18 years or older (20 years or older in Japan and Taiwan) at the time of study entry, had stage IV NSCLC, with an *EGFR* exon 19 deletion (ex19del) or exon 21 substitution (Leu858Arg) mutation, an Eastern Cooperative Oncology Group performance status of 0 or 1, and no CNS metastases. We randomly assigned eligible patients in a 1:1 ratio to receive oral erlotinib (150 mg/day) plus either intravenous ramucirumab (10 mg/kg) or matching placebo once every 2 weeks. Randomisation was done by an interactive web response system with a computer-generated sequence and stratified by sex, geographical region, *EGFR* mutation type, and *EGFR* testing method. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of study treatment. This trial is registered at ClinicalTrials.gov, NCT02411448, and is ongoing for long-term survival follow-up.

Findings Between Jan 28, 2016, and Feb 1, 2018, 449 eligible patients were enrolled and randomly assigned to treatment with ramucirumab plus erlotinib (n=224) or placebo plus erlotinib (n=225). Median duration of follow-up was 20·7 months (IQR 15·8–27·2). At the time of primary analysis, progression-free survival was significantly longer in the ramucirumab plus erlotinib group (19·4 months [95% CI 15·4–21·6]) than in the placebo plus erlotinib group (12·4 months [11·0–13·5]), with a stratified hazard ratio of 0·59 (95% CI 0·46–0·76; p<0·0001). Grade 3–4 treatment-emergent adverse events were reported in 159 (72%) of 221 patients in the ramucirumab plus erlotinib group versus 121 (54%) of 225 in the placebo plus erlotinib group. The most common grade 3–4 treatment-emergent adverse events in the ramucirumab plus erlotinib group were hypertension (52 [24%]; grade 3 only) and dermatitis acneiform (33 [15%]), and in the placebo plus erlotinib group were dermatitis acneiform (20 [9%]) and increased alanine aminotransferase (17 [8%]). Treatment-emergent serious adverse events were reported in 65 (29%) of 221 patients in the ramucirumab plus erlotinib group and 47 (21%) of 225 in the placebo plus erlotinib group. The most common serious adverse events of any grade in the ramucirumab plus erlotinib group were pneumonia (seven [3%]) and cellulitis and pneumothorax (four [2%], each); the most common in the placebo plus erlotinib group were pyrexia (four [2%]) and pneumothorax (three [1%]). One on-study treatment-related death due to an adverse event occurred (haemothorax after a thoracic drainage procedure for a pleural empyema) in the ramucirumab plus erlotinib group.

Interpretation Ramucirumab plus erlotinib demonstrated superior progression-free survival compared with placebo plus erlotinib in patients with untreated *EGFR*-mutated metastatic NSCLC. Safety was consistent with the safety profiles of the individual compounds in advanced lung cancer. The RELAY regimen is a viable new treatment option for the initial treatment of *EGFR*-mutated metastatic NSCLC.

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Introduction

Nearly 85% of primary lung cancers worldwide are of the non-small-cell lung cancer (NSCLC) type, and most patients present with advanced or metastatic disease at diagnosis.[1] *EGFR* mutation-driven NSCLC occurs at frequencies of about 10–20% in white patients and

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See Online for appendix

Research in context

Evidence before this study

We did a literature search on April 1, 2019, for preclinical reports and clinical trials published in English through Jan 1, 2015, using Medline and Ovid, abstracts of major oncology congresses, and the National Cancer Institute's cancer trial registry website (ClinicalTrials.gov). The search terms were "non-small cell lung cancer", "advanced non-small cell lung cancer", "metastatic non-small cell lung cancer", "EGFR", "anti-angiogenesis", "targeted therapy", "VEGFR", "clinical trial", and combinations thereof. Findings showed that epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) had significantly improved efficacy over systemic chemotherapy in *EGFR*-mutated advanced non-small-cell lung cancer (NSCLC) in the first-line setting. Three EGFR TKIs (erlotinib, gefitinib, and afatinib) had been studied and approved in this setting. At the time of RELAY's design and initiation (2014–15), no head-to-head studies had demonstrated that one TKI had superior efficacy to another and the safety profiles were similar. Since erlotinib was the only EGFR TKI that was globally approved at the time, it was chosen as the control for RELAY. EGFR TKIs are associated with inevitable treatment resistance, and most patients will eventually experience loss of clinical benefit. Thus, there is an ongoing unmet need in *EGFR*-mutated metastatic NSCLC for new treatment strategies, such as drug combinations, to delay the emergence of acquired resistance and, therefore, disease progression. In preclinical studies, dual blockade of the EGFR and VEGF pathways improved antitumour activity compared with inhibition of the EGFR pathway alone. Several clinical trials have shown promising results with the anti-VEGFA antibody, bevacizumab, in combination with an EGFR TKI, supporting the potential for dual EGFR and VEGF pathway inhibition. However, conclusions in those trials were limited by small sample sizes, Japanese-only populations, and open-label designs. Ramucirumab is a human IgG1 antibody selective for VEGFR2 that blocks binding of the VEGFA, VEGFC, and VEGFD ligands to VEGFR2, and therefore might have broader effects than does bevacizumab. The RELAY study was done to investigate the efficacy and safety of ramucirumab plus erlotinib versus placebo plus erlotinib in patients with *EGFR*-mutated metastatic NSCLC.

Added value of this study

Compared with placebo plus erlotinib, ramucirumab plus erlotinib led to a significant improvement in progression-free survival, both in the overall population as well as across subgroups, including ex19del versus Leu858Arg and east Asian versus non-east Asian. Additional support for the combination regimen includes the increase in duration of response observed over that of the control group. RELAY, as a large, global, phase 3, placebo-controlled and double-blind trial, provides the strongest clinical evidence reported so far for dual EGFR and VEGF pathway inhibition and establishes dual blockade of VEGFR2 and EGFR pathways as a viable first-line treatment strategy applicable to patients with metastatic NSCLC with common EGFR mutations and no CNS metastases. Additionally, to our knowledge, we recorded the longest median progression-free survival thus far for patients with a baseline Leu858Arg mutation, with similar outcomes reported for ramucirumab plus erlotinib in patients with the ex19del and Leu858Arg mutations. This regimen has a safety profile consistent with the established safety profiles of the individual drugs in the setting of advanced NSCLC. After disease progression, EGFR Thr790Met frequencies were similar between treatment groups—suggesting that the addition of ramucirumab did not affect the erlotinib-associated Thr790Met frequency at disease progression and that treatment with EGFR TKI targeted therapies, such as osimertinib, continues to be an option.

Implications of all the available evidence

Additional first-line treatment options that provide clinically meaningful benefits, including delaying disease progression and the emergence of acquired resistance, are still needed for patients with advanced NSCLC. Expanding the selection of first-line options available for the treatment of metastatic *EGFR*-mutated NSCLC would allow oncologists greater strategic choice on how to use the available drugs, such as sequential EGFR TKI treatment, to provide the best chance of long-term progression-free survival and potentially prolonging time on targeted therapy (thereby delaying time to chemotherapy). In this context, the combination of ramucirumab and erlotinib is a valuable treatment option for patients with *EGFR*-mutated NSCLC.

40–60% in Asian patients.[1,2] 90% of *EGFR* mutations comprise a deletion within exon 19 (ex19del) or a leucine to arginine substitution mutation in exon 21 (Leu858Arg).[2] The presence of these activating *EGFR* mutations in advanced NSCLC is associated with sensitivity to small-molecule EGFR tyrosine kinase inhibitors (TKIs),[2,3] which are the first-line standard-of-care.[2,4–7] However, the degree of benefit might differ by type of mutation, with greater benefit from EGFR TKIs in patients who have NSCLC with the ex19del mutation.[8] Despite durable responses, median progression-free survival with initial therapy for advanced disease is about 1 year with first-generation TKIs (gefitinib and erlotinib).[2] Second-generation and third-generation drugs have shown median progression-free survival of 11·0 months (afatinib), 14·7 months (dacomitinib), and 18·9 months (osimertinib).[4–6,9,10] About 30–60% of patients whose disease progresses on a first-generation or second-generation TKI acquire the EGFR Thr790Met substitution mutation, which is sensitive to osimertinib.[7,11,12] When these targeted therapies are exhausted, chemotherapy, palliative care, or a clinical trial is recommended.[13,14] Immune checkpoint inhibitors have been less effective in *EGFR*-mutated disease and optimal approaches to incorporate such therapies in this population are under investigation.[15] Thus, there is a crucial need for novel

EGFR TKI-based strategies to prolong remission and promote tumour control.

One such strategy supported by preclinical and clinical evidence is the dual blockade of the EGFR and VEGF pathways.[16–21] Preclinical studies have demonstrated that the VEGF and EGFR pathways are interrelated (appendix p 5).[16] In the clinical setting, the dual EGFR and VEGF inhibition approach was initially tested in the BeTa[22] (bevacizumab plus erlotinib *vs* erlotinib alone) and ATLAS[23] (bevacizumab *vs* bevacizumab plus erlotinib) trials. Although in these studies the primary outcome results (progression-free survival for ATLAS and overall survival for BeTa) were negative for the subgroup of patients with wild-type NSCLC, improved efficacy was noted in the *EGFR*-mutated subgroup of patients in both trials, with overall survival hazard ratios (HRs) favouring the anti-VEGFA antibody, bevacizumab, plus erlotinib combination. The JO25567 trial[19] was a randomised, phase 2, open-label study assessing first-line bevacizumab plus erlotinib versus erlotinib alone in 154 Japanese patients with *EGFR*-mutated NSCLC (median progression-free survival 16·0 months [95% CI 13·9–18·1] with the combination *vs* 9·7 months [5·7–11·1] with erlotinib) and was the basis for the regulatory approval of bevacizumab plus erlotinib for first-line treatment of *EGFR*-mutated NSCLC in the EU and for inclusion in EU and Japanese NSCLC treatment guidelines.[14,19,24] These results were confirmed in the phase 3, open-label, NEJ026 trial of 228 Japanese patients (median progression-free survival 16·9 [95% CI 14·2–21·0] in the erlotinib plus bevacizumab group *vs* 13·3 months [11·1–15·3] in the erlotinib group).[18] Given the limitations of those studies (small sample sizes, open-label, and being done in Japan only), the question remains as to whether dual inhibition of EGFR and VEGF pathways is a viable treatment strategy in a global *EGFR*-mutated NSCLC population.

Ramucirumab, a human monoclonal IgG1 antibody, selectively targets VEGFR2, thereby blocking signalling mediated by VEGFA, VEGFC, and VEGFD in NSCLC.[25] Therefore, ramucirumab has the potential for broader antitumour activity than inhibitors of VEGFA.[25] Ramucirumab in combination with docetaxel has gained regulatory approval for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Ramucirumab, as a single drug or in combination with different chemotherapy regimens, has also been approved for second-line gastric or gastro-oesophageal junction adenocarcinoma, colorectal cancer, and hepatocellular carcinoma.[26] The RELAY trial investigating the effect of dual inhibition of EGFR and VEGFR2 in patients with untreated, metastatic, EGFR-mutated NSCLC, initiated in December, 2014, is a global study in three parts: a phase 1b single-arm safety lead-in (part A);[27] a phase 3, randomised, double-blind, placebo-controlled study (part B);[28] and an open-label, single-arm, exploratory east Asian cohort (part C;[29] appendix p 10). This report focuses on the phase 3 primary analysis.

Methods

Study design and participants

This worldwide, double-blind, placebo-controlled phase 3 trial was done in 100 hospitals, clinics, and medical centres in 13 countries (South Korea, Hong Kong, Japan, Taiwan, Canada, France, Germany, Italy, Romania, Spain, Turkey, the USA, and the UK) and was initiated after confirmation of the dose and schedule of ramucirumab with erlotinib in the phase 1b part of the study (started in December, 2014).[27] The protocol is in the appendix (pp 26–182).

Eligibility criteria were age of at least 18 years (≥20 years in Japan and Taiwan) at the time of study entry; stage IV NSCLC as defined by the American Joint Committee on Cancer Staging criteria for lung cancer (patients with recurrent metastatic disease were permitted if adjuvant or neo-adjuvant therapy was completed ≥12 months before the development of metastatic disease); eligible for first-line treatment with erlotinib on the basis of previously documented ex19del or Leu858Arg mutation by local testing; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1; consent to submit tissue samples unless restricted by local regulations; ability to swallow tablets; adequate haematological and organ function as measured in blood for cell counts, bilirubin levels, aspartate aminotransferase and alanine aminotransferase levels, coagulation function, and urinary protein levels; use of adequate contraceptive measures; resolution to grade 1 or less of adverse events due to previous locoregional therapy, surgery, or other anticancer therapy; and life expectancy of at least 3 months and, as judged by the investigator, able to complete at least two cycles of treatment. Exclusion criteria included known EGFR Thr790Met mutation; CNS metastases (in line with contemporary clinical trials in this patient population; JO25567,[19] BELIEF,[30] and ARCHER 1050[6]); third-space fluid requiring frequent drainage; superior vena cava syndrome; clinically relevant congestive heart failure or symptomatic or poorly controlled cardiac arrhythmia; and history of uncontrolled heredity or acquired thrombotic disorder. Complete eligibility criteria and details on the laboratory tests required for assessing eligibility are in the protocol (appendix pp 58–64, 142–145, 152).

The protocol and amendments were approved by the ethics committees of all participating centres and all patients provided written informed consent before study entry. The trial was conducted according to the Declaration of Helsinki, the International Conference on Harmonisation guidelines for good clinical practice, and applicable local regulations.

Randomisation and masking

Investigators enrolled patients after completion of screening procedures (appendix pp 143–145). Eligible

patients were randomly allocated (1:1) to treatment with ramucirumab plus erlotinib or placebo plus erlotinib via an interactive web-response system with a computer-generated random sequence. Randomisation was stratified according to sex (male *vs* female), region (east Asia *vs* other), *EGFR* mutation type (ex19del *vs* Leu858Arg), and local *EGFR* testing method (therascreen [Qiagen; Hilden, Germany] or cobas [Roche; Risch-Rotkreuz, Switzerland] *vs* other PCR and sequencing-based methods).

Physicians, patients, and all clinical study personnel were masked to assigned treatment. For the primary analysis, some sponsor personnel were unmasked to collate, analyse, and communicate data to authors. Physicians, patients, site study personnel, and all sponsor personnel in direct contact with sites will continue to be masked to assigned treatment until after the final overall survival analysis. For masking, allocated treatments were indistinguishable by volume equivalents and provided in containers with identical appearances.

Procedures

Patients received either intravenous ramucirumab 10 mg/kg once every 2 weeks and oral erlotinib 150 mg/day or intravenous placebo once every 2 weeks and oral erlotinib 150 mg/day. Data from other phase 3 ramucirumab trials and pharmacokinetic simulations were used to guide the dose selection in RELAY, with safety and tolerability confirmed in the lead-in phase 1b portion of the RELAY study.[27] To start the next ramucirumab or placebo administration, patients were required to have an acceptable bone marrow reserve, a bilirubin level no greater than the upper limit of normal, and to have recovered from ramucirumab or placebo adverse events to less than grade 2 or equivalent severity to baseline. For ramucirumab dose adjustments, investigators were requested to follow the protocol for guidance. Ramucirumab could be delayed for up to 42 days, allowing for recovery from toxic effects. Three steps of dose reduction of ramucirumab were permitted (to 8 mg/kg, 6 mg/kg, and 5 mg/kg) in the event that a dose reduction criterion was fulfilled. For erlotinib dose adjustments, investigators were requested to refer to the erlotinib package insert or the protocol. Erlotinib could be delayed for up to 3 weeks to allow for recovery from toxic effects. Two steps of dose reduction of erlotinib were permitted (to 100 mg per day and 50 mg per day) if a dose reduction criterion was fulfilled.

Study treatment continued until radiographic progression as assessed by the investigator according to RECIST, version 1.1, or unacceptable toxicity or withdrawal of consent, non-compliance, or investigator decision. Patients who discontinued study treatment were followed up for survival until study completion. Criteria for discontinuation of patients from study participation were investigator decision; if the patient became pregnant during the study; patient decision to withdraw; or if the study were to be stopped for medical, safety, regulatory, or other similar reasons. Tumour assessments (CT or MRI scans), were done within the 28 days before randomisation, every 6 weeks from the first dose of study therapy up to 72 weeks, then every 12 weeks until disease progression or study discontinuation, and at the 30-day short-term follow-up visit (discontinuation criteria are in the appendix pp 38–42). Brain imaging by gadolinium-enhanced MRI was mandated at baseline for all patients to exclude the existence of brain metastases and subsequently performed during the study at the discretion of the investigator, when clinically indicated. Bone scans were performed at baseline, and if abnormal, radiographic imaging was used to confirm. On study, bone scans and PET scans were done if clinically indicated. During the treatment period, complete blood cell counts, serum chemistry, and urine analysis were done every 14 days. Also during treatment, a coagulation profile was performed locally within 4 days before treatment on day 1 of cycle 4 and performed every four cycles or more frequently, as clinically indicated. A pregnancy test, if appropriate, was done every 28 days (appendix pp 146–48).

Patients were assessed for adverse events at each visit and were instructed to contact their physician to report any adverse events between visits. Laboratory and clinical toxic effects were assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Patients had to discontinue all study treatment in the event of disease progression per RECIST version 1.1. The use of any subsequent treatment (start time and type) was at the discretion of the investigator. Disease assessments continued per protocol in patients who discontinued study treatment in the absence of progression.

Pharmacokinetics and immunogenicity were assessed from blood samples obtained at day 1 of specified cycles, before administration of study drugs or 1-h after infusion, or both.

Preplanned confirmatory central *EGFR* testing was conducted centrally using the therascreen assay on archival tissue samples. Thr790Met mutation status was assessed in liquid biopsy samples by Guardant360 (Guardant Health; Redwood City, CA, USA) next-generation sequencing at baseline and at the 30-day follow-up visit.

Patients who discontinued all study treatment because of progressive disease, adverse event, or patient or physician decision were allowed to start any subsequent post-discontinuation treatment at the discretion of the investigator.

Outcomes

The primary endpoint was progression-free survival (defined as the time from randomisation to disease progression or death from any cause) as assessed by investigators according to RECIST, version 1.1. A sensitivity analysis on masked, independent review of

progression-free survival was also done on CT or MRI scans from all patients. Secondary endpoints were safety and toxicity, overall survival (defined as the time from randomisation to date of death from any cause), overall responses (complete responses plus partial responses), disease control (complete responses plus partial responses plus stable disease), duration of response (time from first documented response to the date of objective progression or the date of death, whichever is earlier), pharmacokinetics and immunogenicity, and patient-reported outcomes (on the Lung Cancer Symptom Scale and EuroQol 5-dimension, 5-level questionnaire; these findings will be reported elsewhere). Prespecified exploratory endpoints were progression-free survival 2 (defined as the time from randomisation to second disease progression or death from any cause), time to diagnosis of CNS metastases (defined as the time from randomisation to CNS metastases), and biomarker analyses.

Statistical analysis

Planned enrolment was about 450 patients. The primary analysis was planned to occur when at least 270 progression-free survival events had occurred (40% censoring rate). This number of events provided 80% power to detect progression-free survival superiority of the ramucirumab plus erlotinib group, assuming an HR of 0·71 with type 1 error controlled at 0·05. The assumed median progression-free survival for the placebo plus erlotinib group was 11·0 months. One interim futility analysis was planned for when at least 114 progression-free survival events had occurred with a nominal 1-sided α <0·00001 spent in order to maintain type 1 error.

Patients who did not have a disease progression event or had not died at the time of the analysis were censored at the date of last post-baseline radiological tumour assessment or the date of randomisation if the patient did not have any post-baseline radiological assessment. Patients without tumour progression or death within 14 days of initiating post-discontinuation systemic anticancer treatment were censored. Additional endpoint definitions are provided in the appendix (pp 5–6, 105).

The primary analysis was a stratified log-rank test to compare investigator-assessed progression-free survival between treatment groups. The analysis was stratified by the randomisation strata. The null hypothesis tested was the progression-free survival HR of at least 1 (ramucirumab not superior to placebo) versus the alternative of progression-free survival HR less than 1 (ramucirumab superior to placebo). HRs and 95% CIs were estimated using a stratified Cox proportional hazards model. The assumption of proportional hazards was met for the primary endpoint, which was verified visually through inspection of the graph of log(–log[$S(t)$]) versus log(t) for the two treatment groups, as well as a test of the interaction between treatment and log(time) in the proportional hazards model, which was not significant (Wald's test p=0·34). The Kaplan-Meier method was used to generate progression-free survival curves as well as summary statistics. Similar analyses were conducted for interim overall survival, progression-free survival 2, and for two post-hoc exploratory endpoints: time to discontinuation of any EGFR TKI and time to chemotherapy. HRs and 95% CIs were estimated using an unstratified Cox proportional hazards model for prespecified subgroup analyses to assess internal consistency of study results and assess whether significant treatment heterogeneity exists across any of the subgroups (appendix pp 123–24). The subgroups were as follows: sex (male *vs* female), age (<65 years *vs* ≥65 years), geographical region (east Asia *vs* other), ECOG performance status at baseline (0 *vs* 1), smoking history (ever *vs* never *vs* unknown), disease stage (stage IV *vs* other), liver metastases at baseline (yes *vs* no), *EGFR* mutation type (ex19del *vs* Leu858Arg), and *EGFR* local testing method

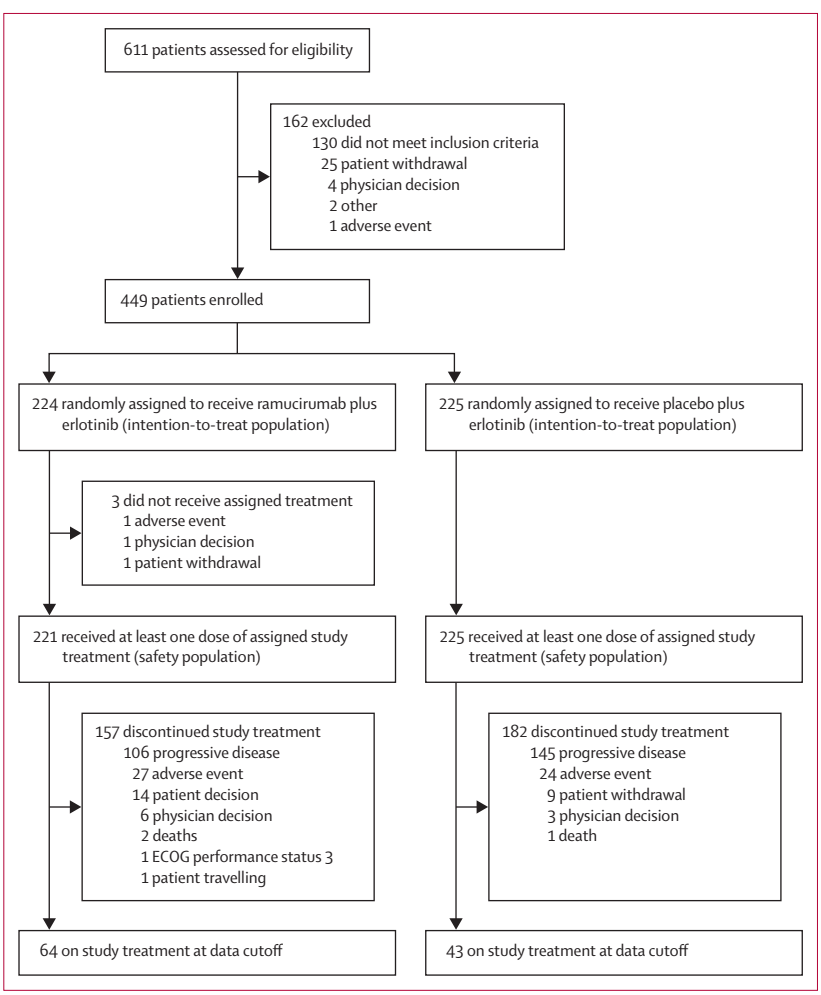

Figure 1: **Trial profile**
In addition to the three patients who did not receive study treatment, five patients in the ramucirumab plus erlotinib group and four patients in the placebo plus erlotinib group had major protocol deviations and were also not included in the per-protocol population. ECOG=Eastern Cooperative Oncology Group.

	Ramucirumab plus erlotinib group (n=224)	Placebo plus erlotinib group (n=225)
Age		
Median (IQR), years	65 (57–71)	64 (56–70)
≥65 years	122 (54%)	111 (49%)
Sex		
Female	141 (63%)	142 (63%)
Male	83 (37%)	83 (37%)
Race*		
Asian	172 (77%)	174 (77%)
White	52 (23%)	48 (21%)
Other	0	3 (1%)
Smoking status		
Ever	64 (29%)	73 (32%)
Never	134 (60%)	139 (62%)
Unknown or missing	26 (12%)	13 (6%)
Geographical region†		
East Asia	166 (74%)	170 (76%)
Other	58 (26%)	55 (24%)
Eastern Cooperative Oncology Group performance status		
0	116 (52%)	119 (53%)
1	108 (48%)	106 (47%)
Pathological diagnosis at study entry		
Adenocarcinoma	215 (96%)	218 (97%)
NSCLC not otherwise specified	9 (4%)	7 (3%)
Disease stage at diagnosis‡		
Stage IV	195 (87%)	189 (84%)
Other	29 (13%)	36 (16%)
***EGFR* mutation type at randomisation (eCRF)**		
Ex19del	123 (55%)	120 (53%)
Leu858Arg	99 (44%)	105 (47%)
Missing	1 (<1%)	0
Other	1 (<1%)	0
***EGFR* testing method**		
Therascreen or cobas	96 (43%)	101 (45%)
Other PCR and sequencing-based methods	127 (57%)	124 (55%)

Data are n (%) unless otherwise specified. NSCLC=non-small-cell lung cancer. eCRF=electronic case report form. *Other included American Indian or Alaska Native, black or African–American, or missing; data were missing for one patient in the placebo plus erlotinib group. †East Asia includes South Korea, Hong Kong, Japan, and Taiwan; other includes Canada, France, Germany, Italy, Romania, Spain, Turkey, the USA, and the UK. ‡All patients were required to have stage IV NSCLC at study entry; patients with recurrent metastatic disease were permitted as long as the adjuvant or neoadjuvant therapy was completed at least 12 months before development of metastatic disease; previous adjuvant or neoadjuvant therapy was not required; at study entry, all patients (as per inclusion criteria) had metastatic stage IV disease (195 [87%] of 224 in the ramucirumab plus erlotinib group *vs* 191 [85%] of 225 in the placebo plus erlotinib group) or recurrent metastatic stage IV disease (29 [13%] *vs* 34 [15%]).

Table 1: **Demographic and clinical characteristics of patients at baseline (intention-to-treat population)**

(therascreen or cobas *vs* other). All tests of interactions were done at a two-sided α level of 0·1. Complete or partial response treatment difference was estimated with the stratified method of Miettinen and Nurminen. Overall response and disease control were reported along with exact 95% CIs based on the normal approximation and compared using the Cochran-Mantel-Haenszel test adjusting for the stratification factors. The unstratified log-rank test was used to compare duration of response (for responders only) and time to diagnosis of CNS metastases between treatment groups. HRs and 95% CIs were estimated using an unstratified Cox proportional hazards model. For the sensitivity analyses, a stratified log-rank test was done for investigator-assessed progression-free survival in the per-protocol population and for the masked independent radiological review of progression-free survival in the intention-to-treat population. HRs and 95% CIs were estimated using a stratified Cox proportional hazards model. Patients with protocol deviations that could potentially affect efficacy conclusions were excluded from the per-protocol population.

Descriptive statistics for treatment-emergent adverse events, pharmacokinetics, and immunogenicity were summarised by study treatment group. Fisher's exact test was used to compare the difference in Thr790Met mutation frequency between groups. Unless otherwise noted, observed data were used and missing data were not imputed or carried forward.

All efficacy endpoints, including the primary investigator-assessed progression-free survival endpoint, were assessed in the intention-to-treat population, which included all randomly assigned patients. Safety was assessed in all patients who received at least one dose of study treatment (safety population). *EGFR* Thr790Met analyses were done in the subset of intention-to-treat patients who had disease progression by data cutoff and had available next-generation sequencing results.

For the progression-free survival sensitivity analysis, imaging scans were reviewed centrally by a masked independent review committee. An external independent data monitoring committee (appendix pp 4, 80, 110, 174–75) assessed unmasked safety data and did a futility analysis. SAS, version 9.4 was used for all statistical analyses.

This trial is registered at ClinicalTrials.gov, number NCT02411448.

Role of the funding source

The funder was involved in study design, data collection, data analysis, data interpretation, and writing of the report. AHZ, BFM, CVG, and KN had full access to all data in the study and KN had final responsibility for the decision to submit for publication.

Results

From Jan 28, 2016, to Feb 1, 2018, 611 patients were screened, of whom 449 (intention-to-treat population) were enrolled and randomly assigned to either ramucirumab plus erlotinib (n=224) or placebo plus erlotinib (n=225; figure 1). Baseline characteristics were balanced between treatment groups (table 1).

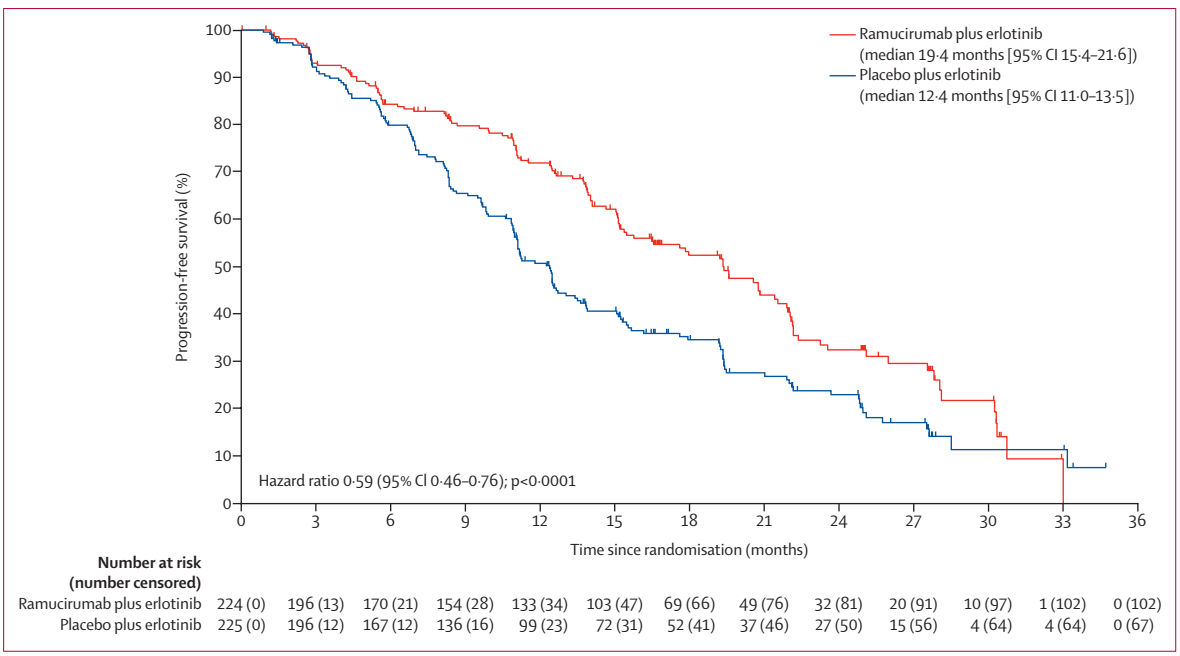

Figure 2: **Kaplan-Meier estimates of investigator-assessed progression-free survival**

At data cutoff, 64 (29%) of 224 patients in the ramucirumab plus erlotinib group and 43 (19%) of 225 in the placebo plus erlotinib group were still on treatment (figure 1). 108 (48%) patients in the ramucirumab plus erlotinib group and 146 (65%) in the placebo plus erlotinib group had disease progression or had died. More than half of patients received subsequent therapy (120 [54%] of 224 in the ramucirumab plus erlotinib group and 156 [69%] of 225 in the placebo plus erlotinib group; appendix p 15).

At a median follow-up of 20·7 months (IQR 15·8–27·2), investigator-assessed median progression-free survival (the primary endpoint) was 19·4 months (95% CI 15·4–21·6) in the ramucirumab plus erlotinib group versus 12·4 months (11·0–13·5) in the placebo plus erlotinib group. The ramucirumab-erlotinib group exhibited a significant reduction in the hazard for progression or death (HR 0·59 [95% CI 0·46–0·76], p<0·0001; figure 2). 1-year progression-free survival was 71·9% (95% CI 65·1–77·6) for the ramucirumab plus erlotinib group and 50·7% (43·7–57·3) for the placebo plus erlotinib group.

The sensitivity analyses of progression-free survival according to masked independent radiological review (440 patients had evaluable scans) and in the per-protocol population (437 evaluable patients) showed progression-free survival results consistent with the primary investigator-assessed progression-free survival analysis. The independently reviewed median progression-free survival in the ramucirumab plus erlotinib group was 16·5 months (95% CI 13·7–19·3), with events in 116 [53%] of 217 patients, versus 11·1 months (9·7–12·7) in the placebo plus erlotinib group, with events in 138 [62%] of 223 patients (stratified HR 0·671 [95% CI 0·518–0·869]; appendix p 11). For the per-protocol sensitivity analysis, median progression-free survival was 19·4 months (95% CI 15·4–21·9) in the ramucirumab plus erlotinib group, with events in 120 (56%) of 216 patients, versus 12·3 months (10·9–13·4) in the placebo plus erlotinib group, with events in 157 (71%) of 221 patients (stratified HR 0·580 [95% CI 0·450–0·747]). A progression-free survival benefit with ramucirumab plus erlotinib was observed in most of the predefined patient subgroups (figure 3). For the EGFR mutation testing subgroups, the difference in HRs was not due to local assay variability, because central testing corroborated local testing results (appendix pp 6–8), and no clear explanation yet exists for the difference observed. Subgroups of patients with ex19del and Leu858Arg mutations also achieved a significant progression-free survival benefit with ramucirumab plus erlotinib versus erlotinib alone, and had similar median progression-free survival to the overall patient population (figure 3; figure 4).

The proportions of patients who achieved either a partial or complete response as assessed by investigators were similar between treatment groups (table 2). The proportions of patients who achieved disease control were high and similar between treatment groups (table 2). The median duration of response was significantly longer in the ramucirumab plus erlotinib group (table 2; appendix p 12).

Overall survival data were immature at data cutoff (370 [82%] of 449 censored). Median interim overall survival was not reached in either group (table 2; appendix p 11). A final analysis is planned when at least

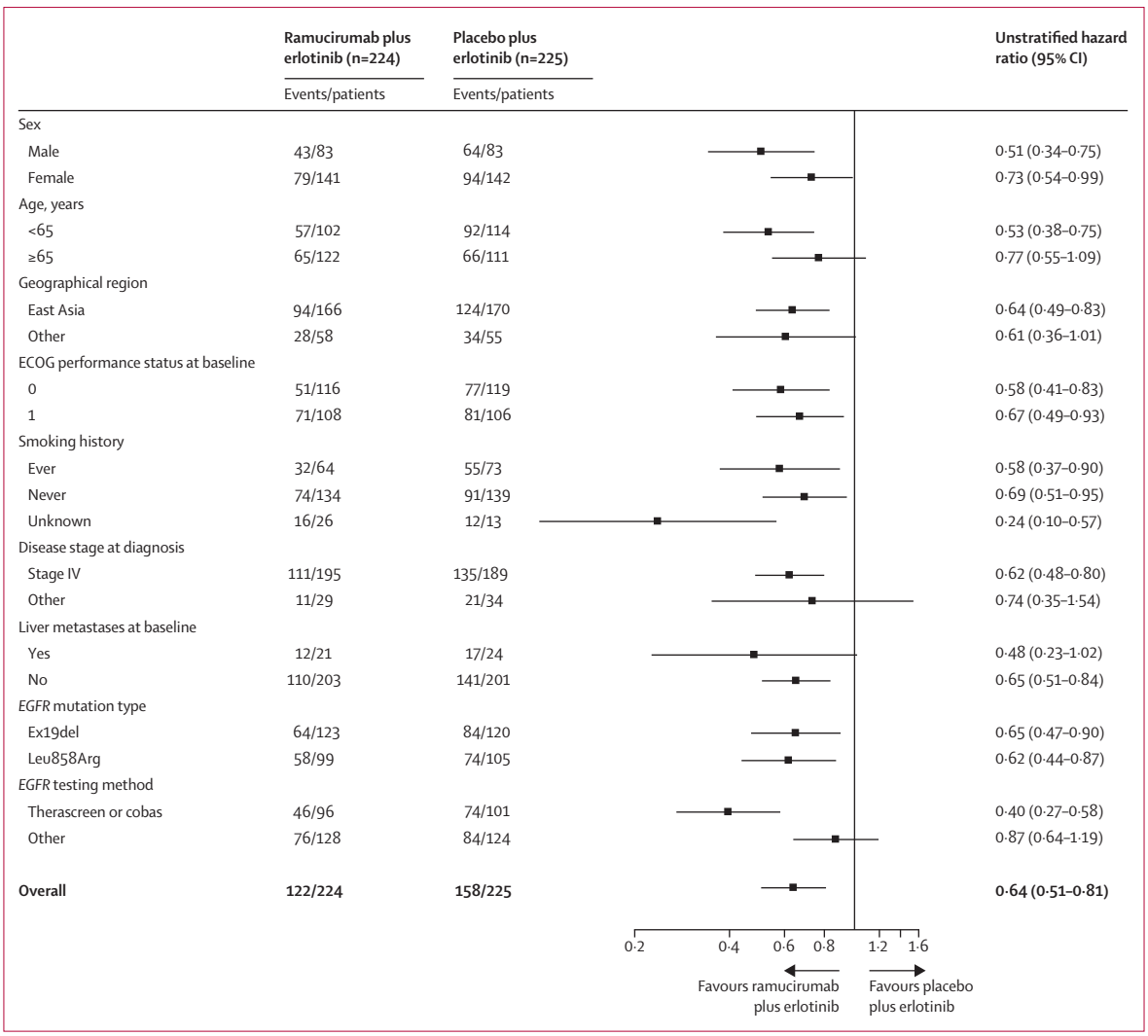

Figure 3: **Subgroup analysis of investigator-assessed progression-free survival**
At study entry, all patients had metastatic or stage IV non-small-cell lung cancer. ECOG=Eastern Cooperative Oncology Group.

300 overall survival events have occurred.

In the absence of mature overall survival data, the effect of first-line ramucirumab plus erlotinib and placebo plus erlotinib on progression-free survival 2, time to discontinuation of any EGFR TKI, and time to chemotherapy were assessed in exploratory analyses. A progression-free survival 2 benefit was observed for the ramucirumab plus erlotinib versus the placebo plus erlotinib group (medians were not reached in either group), with 309 (69%) of 449 censored (appendix p 12). Results for time to discontinuation of any EGFR TKI are in the appendix (p 16), and results for time to chemotherapy are in the appendix (p 8).

The time to diagnosis of CNS metastases endpoint was prespecified in the statistical analysis plan. However, with only ten events (two in the ramucirumab plus erlotinib group and eight in the placebo plus erlotinib group), this analysis was not done.

Median duration of exposure to ramucirumab or placebo was 11·0 months (4·2–15·6) in the ramucirumab plus erlotinib group versus 9·7 months (3·7–15·6) in the placebo plus erlotinib group (appendix p 17). Dose reductions of ramucirumab or placebo due to treatment-emergent adverse events occurred in 23 (10%) of 221 patients versus four (2%) of 225 patients (appendix p 18). Proteinuria was the most common reason for dose reductions of ramucirumab in the ramucirumab plus erlotinib group (18 [8%] of 221 patients), with no placebo dose reductions due to proteinuria in the placebo plus erlotinib group (appendix pp 8, 18). 28 (13%) of 221 patients in the ramucirumab plus erlotinib group and 24 (11%) of 225 patients in the placebo plus erlotinib group discontinued all study treatment because of treatment-emergent adverse events (appendix p 19). The most common treatment-emergent adverse events leading to discontinuation were increased alanine

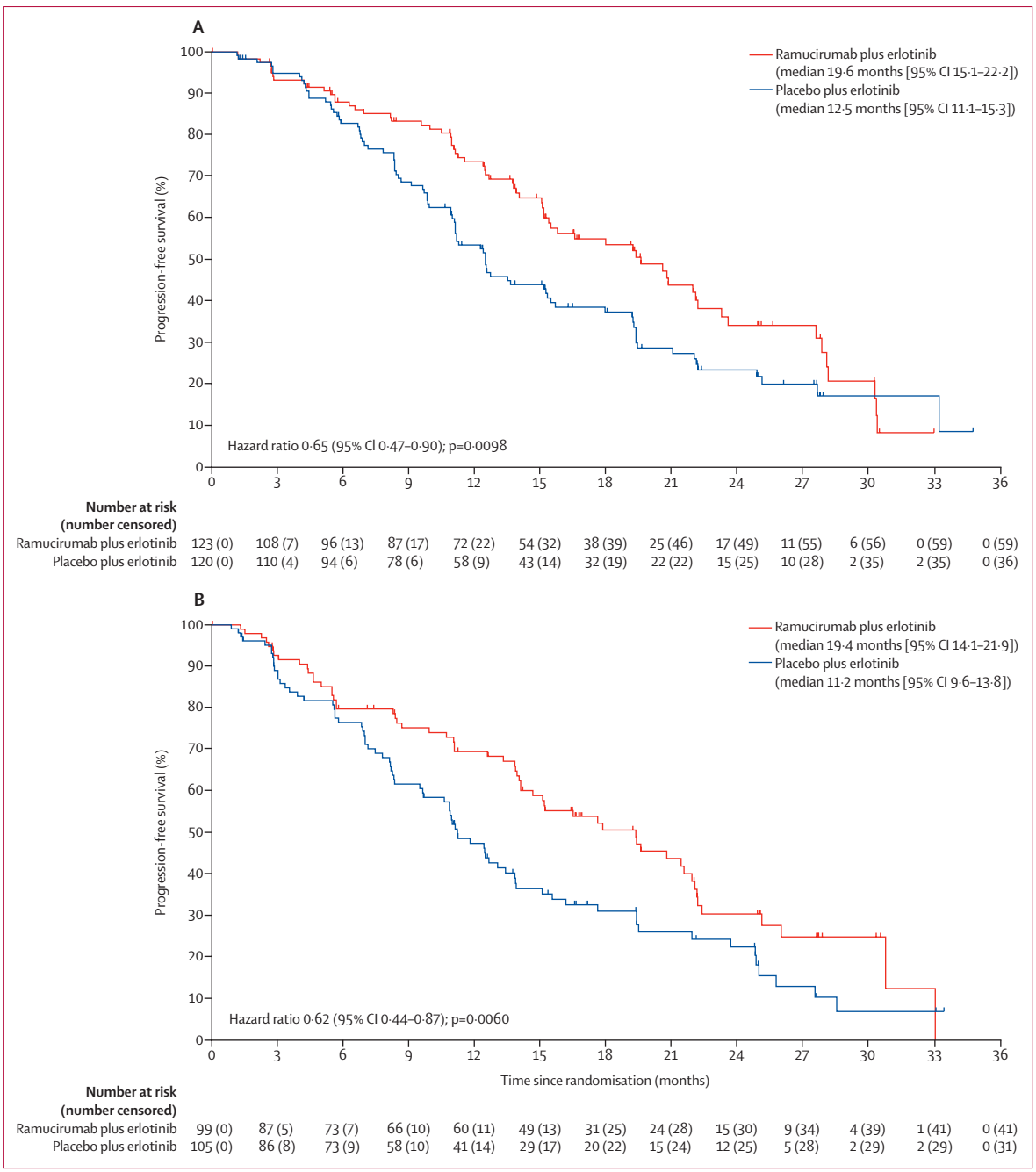

Figure 4: **Kaplan-Meier estimates of investigator-assessed progression-free survival of patients with a baseline ex19del (A) or Leu858Arg (B) mutation**

aminotransferase (n=3), paronychia (n=3), dermatitis acneiform (n=2), and proteinuria (n=2) in the ramucirumab plus erlotinib group and increased alanine aminotransferase (n=4), abnormal liver function (n=3), embolism (n=2), interstitial lung disease (n=2); and pustular rash (n=2) in the placebo plus erlotinib group.

All patients in the safety population had at least one treatment-emergent adverse event (table 3; appendix pp 19–22).

159 (72%) of 221 patients in the ramucirumab plus erlotinib group and 121 (54%) of 225 in the placebo plus erlotinib group had grade 3 or worse treatment-emergent adverse events (appendix p 19). The most common grade 3 or worse treatment-emergent adverse events were hypertension (52 [24%]) and dermatitis acneiform (33 [15%]) in the ramucirumab plus erlotinib group and dermatitis acneiform (20 [9%]) and increased alanine aminotransferase (17 [8%]) in the placebo plus erlotinib

	Ramucirumab plus erlotinib group (n=224)	Placebo plus erlotinib group (n=225)
Best overall response		
Complete response	3 (1%)	2 (1%)
Partial response	168 (75%)	166 (74%)
Stable disease	42 (19%)	47 (21%)
Progressive disease	3 (1%)	6 (3%)
Non-evaluable*	8 (4%)	4 (2%)
Overall response†		
Patients with overall response	171 (76%)	168 (75%)
95% CI	71–82	69–80
Stratified p value	..	0·741
Disease control‡		
Patients with disease control	213 (95%)	215 (96%)
95% CI	(92–98)	(93–98)
Stratified p value	..	1·00
Duration of response		
Number of events, n/N responders (%)	101/171 (59%)	128/168 (76%)
Median (95% CI), months	18·0 (13·9–19·8)	11·1 (9·7–12·3)
Unstratified p value	..	0·0003
Unstratified hazard ratio (95% CI)	..	0·62 (0·48–0·81)
Interim overall survival analysis		
Number of events, n (%)	37 (17%)	42 (19%)
Median (95% CI), months	Not reached	Not reached
Stratified p value	..	0·421
Stratified hazard ratio (95% CI)	..	0·83 (0·53–1·30)
1-year overall survival (95% CI)	93% (89–96)	94% (90–96)
2-year overall survival (95% CI)	83% (77–88)	79% (72–85)

Responses were investigator assessed according to RECIST, version 1.1. RECIST=Response Evaluation Criteria In Solid Tumors. *Of the eight patients who were not evaluable in the ramucirumab plus erlotinib group, the reasons were not treated with study treatment (n=3), no post-baseline assessments (n=3; with one death without progressive disease and one withdrawal); and incomplete response assessment (n=2); for the four patients who were not evaluable in the placebo group, the reason was incomplete response assessment. †Complete or partial response; treatment difference was estimated with the stratified method of Miettinen and Nurminen. ‡Complete response, partial response, or stable disease; CIs were based on the normal approximation; p values were calculated by Exact Cochran-Mantel-Haenszel test stratified by the randomisation strata: region, gender, *EGFR* mutation type, and *EGFR* testing method.

***Table 2*: Secondary efficacy endpoints (intention-to-treat population)**

group. Grade 3 or worse treatment-emergent adverse events reported in more than 5% of patients and with at least a five percentage point difference in the ramucirumab plus erlotinib group versus the placebo plus erlotinib group were hypertension (52 [24%] in the ramucirumab plus erlotinib group *vs* 12 [5%] in the placebo plus erlotinib group), diarrhoea (16 [7%] *vs* three [1%]), and dermatitis acneiform (33 [15%] *vs* 20 [9%]), all of which were of maximum grade 3 severity (table 3; appendix pp 20–21).

Although no new toxic effects were identified, ramucirumab did increase the incidence or severity of several erlotinib associated adverse events, namely dermatitis acneiform and diarrhoea (increased grade 3 incidence; no grade 4 or 5 events) and low-grade stomatitis, alanine aminotransferase and aspartate aminotransferase increases, and alopecia (table 3; appendix pp 20–21). Four (2%) patients in the ramucirumab plus erlotinib group and seven (3%) in the placebo plus erlotinib group had interstitial lung disease events (including pneumonitis; table 3). Overall, a similar proportion of Asian and non-Asian patients had interstitial lung disease: nine (3%) of 344 Asian patients and two (2%) of 102 non-Asian patients. Adverse events of special interest specific to anti-angiogenic drugs had an increased incidence in the ramucirumab plus erlotinib group: hypertension (100 [45%] in the ramucirumab plus erlotinib group *vs* 27 [12%] in the placebo plus erlotinib group; no grade 4 or 5), any grade proteinuria (76 [34%] *vs* 19 [8%]), and low-grade (grade 1–2) bleeding or haemorrhage events (117 [53%] *vs* 55 [24%]; mainly epistaxis; table 3; appendix p 9).

The proportion of patients with any-grade treatment-emergent serious adverse events was higher in the ramucirumab plus erlotinib group (65 [29%] of 221) than in the placebo plus erlotinib group (47 [21%] of 225; appendix p 23). Treatment-related serious adverse events of any grade were reported in 34 (15%) patients in the ramucirumab plus erlotinib group and 26 (12%) in the placebo plus erlotinib group.

37 (17%) of 221 patients in the ramucirumab plus erlotinib group and 42 (19%) of 225 in the placebo plus erlotinib group died before data cutoff (appendix p 24). Six deaths due to treatment-emergent adverse events occurred on therapy or within 30 days of treatment discontinuation in the ramucirumab plus erlotinib group, whereas none occurred in the placebo plus erlotinib group. One death on study therapy (haemothorax) was considered related to study drug and occurred in a patient in the ramucirumab plus erlotinib group who had had a thoracic drainage procedure for a pleural empyema 6 days earlier.

Ramucirumab geometric mean concentrations before infusion (trough) were increasing (39·6 μg/mL [coefficient of variation 32%; n=185] at cycle 2, 68·5 μg/mL [37%; n=145] at cycle 4, 85·7 μg/mL [32%; n=110] at cycle 7, and 99·4 μg/mL [31%; n=59] at cycle 14). Peak geometric mean concentrations (1 h after infusion) at the first infusion was 210 μg/mL (coefficient of variation 19%; n=194) and was 319 μg/mL (26%; n=53) at the 14th infusion. Ramucirumab did not appear to affect the pharmacokinetics of erlotinib (data not shown).

No new or significant safety findings regarding treatment-emergent antidrug antibodies were reported (data not shown).

In line with the exclusion of patients with known Thr790Met at study enrolment, no Thr790Met mutations

	Ramucirumab plus erlotinib group (n=221)			Placebo plus erlotinib group (n=225)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
Treatment-emergent adverse events occurring in at least 20% of participants*						
Diarrhoea	139 (63%)	16 (7%)	0	157 (70%)	3 (1%)	0
Dermatitis acneiform	116 (52%)	33 (15%)	0	133 (59%)	20 (9%)	0
Paronychia	109 (49%)	9 (4%)	0	107 (48%)	7 (3%)	0
Hypertension	48 (22%)	52 (24%)	0	15 (7%)	12 (5%)	0
Alanine aminotransferase increased	75 (34%)	17 (8%)	2 (1%)	53 (24%)	14 (6%)	3 (1%)
Stomatitis	88 (40%)	4 (2%)	0	79 (35%)	3 (1%)	0
Aspartate aminotransferase increased	81 (37%)	11 (5%)	0	48 (21%)	9 (4%)	1 (<1%)
Dry skin	82 (37%)	1 (<1%)	0	86 (38%)	5 (2%)	0
Alopecia	75 (34%)	0	0	44 (20%)	0	0
Proteinuria	69 (31%)	6 (3%)	0	19 (8%)	0	0
Epistaxis	74 (33%)	0	0	27 (12%)	0	0
Blood bilirubin increased	65 (29%)	3 (1%)	0	68 (30%)	2 (1%)	0
Decreased appetite	51 (23%)	6 (3%)	0	43 (19%)	4 (2%)	0
Nausea	55 (25%)	2 (1%)	0	42 (19%)	2 (1%)	0
Pruritus	49 (22%)	2 (1%)	0	64 (28%)	2 (1%)	0
Oedema peripheral	48 (22%)	2 (1%)	0	10 (4%)	0	0
Cough	47 (21%)	1 (<1%)	0	35 (16%)	0	0
Pyrexia	47 (21%)	0	0	27 (12%)	1 (<1%)	0
Rash	37 (17%)	2 (1%)	0	49 (22%)	5 (2%)	0
Treatment-emergent adverse events of special interest†						
Bleeding or haemorrhage events	117 (53%)	2 (1%)	1 (<1%)	55 (24%)	4 (2%)	0
Epistaxis	74 (33%)	0	0	27 (12%)	0	0
Gum bleeding	19 (9%)	0	0	3 (1%)	0	0
Gastrointestinal haemorrhage events	20 (9%)	2 (1%)	1 (<1%)	5 (2%)	1 (<1%)	0
Anal haemorrhage	6 (3%)	0	0	1 (<1%)	0	0
Haemorrhoidal haemorrhage	5 (2%)	0	0	4 (2%)	0	0
Pulmonary haemorrhage events	14 (6%)	0	0	3 (1%)	1 (<1%)	0
Haemoptysis	12 (5%)	0	0	1 (<1%)	1 (<1%)	0
Hypertension	48 (22%)	52 (24%)	0	15 (7%)	12 (5%)	0
Proteinuria	70 (32%)	6 (3%)	0	19 (8%)	0	0
Venous thromboembolic events	4 (2%)	3 (1%)	0	4 (2%)	5 (2%)	0
Congestive heart failure	2 (1%)	2 (1%)	0	1 (<1%)	0	0
Fistula	1 (<1%)	1 (<1%)	0	0	0	0
Healing complications	2 (1%)	0	0	1 (<1%)	0	0
Arterial thromboembolic events	1 (<1%)	1 (<1%)	0	0	0	0
Gastrointestinal perforation	1 (<1%)	0	0	0	0	0
Liver failure, injury, or infection events	109 (49%)	27 (12%)	4 (2%)	92 (41%)	21 (9%)	7 (3%)
Alanine aminotransferase increased	75 (34%)	17 (8%)	2 (1%)	53 (24%)	14 (6%)	3 (1%)
Aspartate aminotransferase increased	81 (37%)	11 (5%)	0	48 (21%)	9 (4%)	1 (<1%)
Infusion-related reactions‡	6 (3%)	0	0	4 (2%)	0	0
Other treatment-emergent adverse events of interest						
Interstitial lung disease or pneumonitis§	3 (1%)	1 (<1%)	0	4 (2%)	2 (1%)	0

Data are n (%). *No deaths were reported due to treatment-emergent adverse events occurring in at least 20% of participants; one death occurred on study and was because of a pulmonary haemorrhage event of haemothorax; one patient in the placebo group had a fatal event of interstitial lung disease more than 30 days after treatment discontinuation. †Adverse events of special interest are those associated with ramucirumab treatment in previous clinical trials of non-small-cell lung cancer, gastric cancer, urothelial cancer, and hepatocellular carcinoma. ‡Infusion-related reactions include anaphylactic reactions, hypersensitivity, and angio-oedema occurring within 24 h of ramucirumab or placebo infusion. §Data for interstitial lung disease and pneumonitis are here because these are related and previously associated with EGFR tyrosine kinase inhibitors.

Table 3: **Treatment-emergent adverse events, any causality, and adverse events of special interest (ramucirumab) in the safety population**

were detected centrally at baseline. Post-progression results at the 30-day follow-up were available for 190 (69%) of the 275 patients whose disease progressed before data cutoff. Given that different criteria are applied in the literature to define the population for this type of analysis, two approaches are presented (table 4). The first

	Ramucirumab plus erlotinib group	Placebo plus erlotinib group	p value*
Population 1†			
Patients with Thr790Met detected in 30-day follow-up sample	17/68	31/103	..
Post-progression Thr790Met frequency (95% CI)	25% (16–36)	30% (22–40)	0·492
Population 2‡			
Patients with Thr790Met detected in 30-day follow-up sample	19/44	35/75	..
Post-progression Thr790Met frequency (95% CI)	43% (30–58%)	47% (36–58%)	0·849

Data are n/N or % (95% CI). EGFR=epidermal growth factor receptor. NGS=next-generation sequencing. *Two-sided Fisher's exact test. †Analysis population 1 consisted of patients with baseline results and with post-progression 30-day follow-up results; no patients with baseline central NGS Guardant360 results were positive for EGFR Thr790Met at baseline; however, baseline NGS results were not available for 19 of the 190 patients with post-progression 30-day follow-up NGS results. ‡Analysis population 2 consisted of patients with EGFR activating mutation detected in the post-progression 30-day follow-up sample; EGFR activating mutations (ex19del or Leu858Arg) could not be detected in 71 of 190 patients with post-progression 30-day follow-up NGS results.

Table 4: **Post-progression Thr790Met frequency at the 30-day follow-up using NGS**

analysis includes patients who had both a baseline and a 30-day follow-up central next-generation sequencing result. Treatment-emergent *EGFR* Thr790Met frequencies were similar between groups. A second analysis was performed that limited the population to patients with a detectable *EGFR* activating mutation at 30-day follow-up. This approach ensured that the patient population had tumours that were shedding DNA, so that any Thr790Met in the tumour could be detected in the liquid biopsy sample. This analysis also found similar Thr790Met frequencies between treatment groups. Post-progression Thr790Met frequencies were assessed according to the number of treatment cycles received before the 30-day follow-up visit (appendix p 13).

Discussion

RELAY showed that in patients with previously untreated metastatic *EGFR*-mutated NSCLC without CNS metastases, ramucirumab plus erlotinib treatment resulted in a significant improvement in progression-free survival, with a median progression-free survival of 19·4 months (95% CI 15·4–21·6) for ramucirumab plus erlotinib versus 12·4 months (95% CI 11·0–13·5) with placebo plus erlotinib. The sensitivity analyses results support the robustness of the investigator-based statistical results and conclusions with respect to progression-free survival. The RELAY study population is representative of that seen in clinical practice, with a high representation of women, east Asian people, never smokers, and histology of lung adenocarcinomas.

A consistent progression-free survival benefit was observed in both east Asian and non-east Asian patients. Notably, the magnitude of progression-free survival benefit observed for Leu858Arg, usually associated with poorer treatment outcomes relative to the ex19del, was similar to that of ex19del, with, to our knowledge, the longest median progression-free survival reported thus far for a subgroup of patients with Leu858Arg, albeit in this population without CNS metastases. Clinically relevant improvements with ramucirumab plus erlotinib treatment were consistently observed across secondary and exploratory endpoints (including duration of response, progression-free survival 2, and time to discontinuation of any EGFR TKI). The RELAY study establishes that the dual blockade of VEGFR2 and EGFR pathways is a viable first-line treatment strategy applicable to both east Asian and non-east Asian populations with metastatic NSCLC with common EGFR mutations.

Since RELAY was initiated, the *EGFR*-mutated NSCLC treatment landscape has evolved with the approval of osimertinib, a generally well-tolerated first-line EGFR TKI therapy providing a median progression-free survival of 18·9 months (95% CI 15·2–21·4) in the FLAURA study.[5] Presence of CNS metastases is a well-known adverse prognostic factor and common site of disease progression in *EGFR*-mutated NSCLC. Limitations of the RELAY study are the biweekly visits to the hospital for a treatment infusion and the exclusion of patients with CNS metastases, which might have enriched our population for patients with better prognoses. This exclusion criterion was similar to other contemporary clinical trials in this setting (ARCHER 1050,[6] JO25567,[19] and BELIEF[30]) and consistent with the patient population treated with erlotinib in clinical practice. The subset of FLAURA patients without brain metastases, more similar to patients included in RELAY, had a median progression-free survival of 19·1 months (95% CI 15·2–23·5). In RELAY, brain imaging was required at baseline, and subsequently done when clinically indicated at the discretion of investigator. The number of patients with CNS metastases as the first site of progression was low in both treatment groups (a total of ten patients: two in the ramucirumab plus erlotinib group and eight in the placebo plus erlotinib group). Additionally, the study was not powered for subgroup analyses. As such, the results of the subgroup analyses should be interpreted with caution.

As per the RELAY protocol, patients were required to discontinue all study treatment at the time of RECIST-defined progression. This protocol differs from clinical practice and from other studies, where treatment beyond the point of RECIST progression is allowed as long as there is continued benefit as judged by the investigator. In FLAURA,[5] 187 (67%) of 279 patients in the osimertinib group and 194 (70%) of 277 in the standard EGFR TKI group continued study treatment beyond RECIST progression. In RELAY, 61 (51%) of 120 patients in the ramucirumab plus erlotinib group and 55 (35%) of 156 patients in the placebo plus erlotinib group received erlotinib as first subsequent therapy after RECIST progression on study treatment, which might have led to underestimating the potential benefit for progression-free survival 2.

At the time of data cutoff, overall survival data remain immature, but do not demonstrate a detrimental effect of

ramucirumab plus erlotinib in the interim overall survival analysis. Overall survival data for the FLAURA[5] and NEJ026[18] studies are similarly immature, but in the JO25567 trial,[31] the overall survival analysis was insufficiently powered because only half of the patients consented to long-term survival follow-up. Thus, it remains unknown whether bevacizumab plus erlotinib prolongs overall survival. More insights on overall survival in RELAY will take time. Meanwhile, we assessed progression-free survival 2, which is a potential surrogate for overall survival.[32] The preliminary progression-free survival 2 data suggest that the ramucirumab plus erlotinib treatment effect was preserved after discontinuation of study treatment and that patients maintained a benefit from the treatment combination through their second progression.

Not unexpectedly, the combination of ramucirumab plus erlotinib increased the incidence of several treatment-emergent adverse events relative to placebo plus erlotinib; however, differences were mostly driven by grade 1–2 events. Treatment-emergent adverse events in RELAY were largely manageable with dose modifications and supportive therapies. Pharmacological class-related effects of antiangiogenic drugs, namely hypertension, proteinuria, and bleeding events, were reported at higher frequencies in the ramucirumab plus erlotinib group than in the placebo plus erlotinib group but were mainly grade 1 and 2 in severity, except for hypertension. More grade 3 erlotinib-associated toxicities occurred (diarrhoea and dermatitis acneiform) and frequencies of grade 1–2 erlotinib-associated toxicities such as alanine aminotransferase and aspartate aminotransferase were greater in the ramucirumab plus erlotinib group than in the placebo plus erlotinib group. A longer treatment exposure to erlotinib might have contributed to this increase. Overall, the additional toxicity with ramucirumab plus erlotinib did not adversely affect the patients' ability to continue study treatment, as shown by longer durations of treatment for both study drugs in the ramucirumab plus erlotinib group, similar high dose intensity, and similar frequencies of study treatment discontinuations due to treatment-emergent adverse events, grade 3 or worse adverse events, and serious adverse events between treatment groups.

Interstitial lung disease is a well-known adverse event of EGFR TKIs and is frequently reported in Japanese patients. In RELAY, the incidence of interstitial lung disease-like events was low for the ramucirumab plus erlotinib group. This result is similar to other EGFR TKI plus anti-VEGF combination trials,[5,18,19] whereas higher rates are reported for single-drug EGFR TKIs.[5,6,18,19] In FLAURA, all-grade interstitial lung disease-like events were reported in 11 (4%) of the 279 patients in the intention-to-treat population[5] and eight (12%) of the 65 patients in the Japanese subset[33] in the osimertinib group, and in six (2%) of 277 in the intention-to-treat population[5] and one (2%) of 55 in the Japanese subset[33] in the standard EGFR TKI group. The low incidence of interstitial lung disease in EGFR TKI plus anti-VEGF combination studies might be due to a potential protective effect of VEGFR inhibition in lung tissue.[34] At least one clinical trial is ongoing (NCT02789345) that is exploring the combination of ramucirumab plus osimertinib, which might provide additional data with respect to interstitial lung disease events.

The most common mechanism of resistance to first-line treatment with first-generation and second-generation EGFR TKIs is the Thr790Met mutation. In RELAY, the proportions of patients with Thr790Met at progression were similar between treatment groups. These data suggest that the addition of ramucirumab to erlotinib does not prevent emergence of the Thr790Met resistance mechanism and that subsequent treatment with a Thr790Met-targeting drug such as osimertinib might remain a viable therapeutic option as next-line therapy. The cumulative incidence of Thr790Met frequencies suggests the possibility that ramucirumab plus erlotinib might delay the emergence of this resistance mechanism. Targetable mutations have a key role in identifying treatment options in NSCLC. Additional biomarker analyses are ongoing and the results will be reported separately.

In conclusion, ramucirumab plus erlotinib provided superior progression-free survival versus placebo plus erlotinib in first-line metastatic *EGFR*-mutated NSCLC. Safety was consistent with the established safety profiles of the individual compounds and a metastatic NSCLC population. The RELAY regimen is therefore a viable new treatment option for the initial treatment of patients with metastatic *EGFR*-mutated NSCLC.

Contributors

KN, MR, and EBG contributed to the study design, treated patients, collected and interpreted data, wrote the first draft of the report with assistance from Eli Lilly medical writers, and critically reviewed, wrote, or edited additional versions. TS, MN, SPA, LP-A, C-HC, KP, SN, EN, FI, KY, J-YS, KHA, and DM-S treated patients, collected and interpreted data, and contributed to critical review and writing or editing of the report. SE, BF-M, and CV-G collected and interpreted data and collaborated on the writing or editing of the report. AZ contributed statistical analyses and collaborated on writing or editing of the report. All authors agreed to the final version and submission to the journal.

Declaration of interests

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Data sharing

Eli Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once they are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the Vivli website.

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