Ramucirumab or placebo plus erlotinib in EGFR-mutated, metastatic non-small-cell lung cancer: East Asian subset of RELAY

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Abstract
In the global phase III RELAY study, ramucirumab plus erlotinib (RAM + ERL) demonstrated superior progression-free survival (PFS) to placebo plus erlotinib (PL + ERL) in untreated patients with epidermal growth factor receptor (EGFR) mutation-positive metastatic non-small-cell lung cancer (NSCLC) (hazard ratio [HR] [95% CI]: 0.59 [0.46-0.76]). This prespecified analysis assessed RAM + ERL efficacy and safety in the RELAY subset enrolled in East Asia (Japan, Taiwan, South Korea, Hong Kong). Randomized (1:1) patients received oral ERL (150 mg/d) plus intravenous RAM (10 mg/kg) or PL Q2W. Primary endpoint was PFS (investigator-assessed). Key secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), overall survival (OS), and safety. Exploratory endpoints included biomarker analyses and time to second progression (PFS2). Median PFS was 19.4 vs 12.5 mo for RAM + ERL (n = 166) vs PL + ERL (n = 170) (HR: 0.636 [0.485-0.833]; P = .0009). The 1-y PFS rate was 72.4% vs 52.2%, respectively. PFS benefit was consistent in most subgroups, including by EGFR mutation (Ex19del, Ex21.L858R). ORR and DCR were similar in both arms, but median DoR was longer with RAM + ERL. OS and PFS2 were immature at data cut-off (censoring rates, 81.2%-84.3% and 64.1%-70.5%, respectively). Grade ≥ 3 treatment-emergent adverse events were more frequent with RAM + ERL (70.7%) than PL + ERL (49.4%). Adverse events leading to treatment discontinuation were similar.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CNS, central nervous system; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ERL, erlotinib; Ex19del, Ex21.L858R, EGFR exon 19 deletion; Ex21.L858R, EGFR exon 21 point mutation; GI, gastrointestinal; HR, hazard ratio; ILD, interstitial lung disease; ITT, intention-to-treat; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; PFS2, time to second progression; PL, placebo; PR, partial response; RAM, ramucirumab; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

See RELAY Study Investigators in Appendix I.

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in both arms (RAM + ERL, 13.3%; PL + ERL, 12.9%), as were post-progression *EGFR* T790M mutation rates (43%; 50%). With superior PFS over PL + ERL and safety consistent with the overall RELAY population, RAM + ERL is a viable treatment option for *EGFR*-mutated metastatic NSCLC in East Asia.

**KEYWORDS**
East Asia, epidermal growth factor receptor, erlotinib hydrochloride, non-small-cell lung cancer, ramucirumab

### 1 | INTRODUCTION

In East Asia, lung cancer is the most frequently diagnosed cancer and the leading cause of cancer death.\(^\text{1}\) In non-small-cell lung cancer (NSCLC), activating mutations in the epidermal growth factor receptor (EGFR) gene are more prevalent in Asian patients than non-Asian patients, occurring in 40%-60% of East Asian patients and 10%-20% of Caucasian patients.\(^\text{2}\) EGFR tyrosine kinase inhibitor (TKI) therapy is the first-line standard of care in patients with advanced NSCLC with activating EGFR mutations,\(^\text{3,4}\) and many of the landmark trials in the development of EGFR TKIs were conducted in Asian patients.\(^\text{2}\) Approximately 90% of *EGFR* mutations occur in exon 19 (exon 19 deletion [Ex19del]) or exon 21 (exon 21 point mutation [Ex21.L858R]), with Ex21.L858R more prevalent in East Asian patients than in Caucasian patients.\(^\text{5,6}\) Although the presence of activating EGFR mutations predicts sensitivity to EGFR TKIs, the treatment benefit may differ depending on *EGFR* mutation type.\(^\text{6}\) In addition, Asian ethnicity itself is a predictor of better outcomes after first-line EGFR TKI treatment, independent of *EGFR* mutation type or other factors often associated with Asian patients, such as smoking status.\(^\text{7}\) Regardless of initial response, acquired resistance to EGFR TKIs results in treatment failure.\(^\text{8}\) The most common mechanism of resistance to first- and second-generation EGFR TKIs is acquisition of the *EGFR* T790M point mutation, which occurs in 30%-60% of patients.\(^\text{9,12}\) The mechanisms of resistance to third-generation EGFR TKIs, such as osimertinib, are heterogeneous and difficult to target.\(^\text{13}\) Therefore, there is a need for treatment strategies that enhance the efficacy of EGFR TKIs in patients with *EGFR*-mutated NSCLC.

A potential strategy to further improve outcomes in patients with *EGFR*-mutated NSCLC is dual inhibition of the EGFR and vascular endothelial growth factor (VEGF) signaling pathways, which is supported by preclinical and clinical data.\(^\text{14-17}\) Ramucirumab is a human immunoglobulin G1 monoclonal antibody against VEGF receptor 2. In the global phase III RELAY study, addition of ramucirumab to erlotinib significantly improved progression-free survival (PFS) compared with erlotinib plus placebo in 449 untreated patients with *EGFR*-mutated metastatic NSCLC (median PFS: 19.4 vs 12.4 mo; hazard ratio [HR]: 0.59; 95% confidence interval [CI]: [0.46-0.76]; \(P < .0001\)).\(^\text{18}\) There was a consistent clinical benefit for the combination regimen across subgroups, including by *EGFR* mutation type, and for duration of response (DoR) and time to second progression (PFS2).\(^\text{18}\) The safety profile was manageable and consistent with the established safety profile of the individual treatment components or with events related to metastatic *EGFR*-mutated NSCLC.\(^\text{18}\) In addition, *EGFR* T790M mutation rates at disease progression were similar between treatment arms, suggesting that the addition of ramucirumab did not prevent emergence of T790M in patients receiving erlotinib. These results support the RELAY regimen as a new treatment option for the initial treatment of patients with *EGFR*-mutated, advanced NSCLC.\(^\text{4,19}\)

This prespecified subset analysis assessed the efficacy and safety of ramucirumab in combination with erlotinib in East Asian patients who were enrolled in the RELAY study at East Asian sites.

### 2 | MATERIALS AND METHODS

**2.1 | Study design**

Full details of the RELAY study design have been published.\(^\text{18}\) The RELAY study was a global, double-blind, placebo-controlled, phase III study conducted in 100 hospitals and clinics in 13 countries (www.clinicaltrials.gov; NCT02411448). Analysis of the East Asian subset was a prespecified subgroup analysis of patients enrolled in Japan, South Korea, Taiwan, and Hong Kong. The study protocol was approved by the ethics review board of each site and was conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, Good Clinical Practice guidelines, and applicable local guidelines. All patients provided written informed consent before study entry.

**2.2 | Study population**

Patients with stage IV NSCLC (defined by the American Joint Committee on Cancer Staging criteria for lung cancer, 7th edition\(^\text{20}\)) who were eligible for first-line treatment with erlotinib on the basis of previously documented *EGFR* Ex19del or Ex21.L858R mutation by local testing were eligible for inclusion in the study. The main inclusion criteria were age ≥18 y (≥20 y in Japan and Taiwan), measurable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST), and Eastern Cooperative Oncology Group performance

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status of 0 or 1. The main exclusion criteria were known EGFR T790M mutation and central nervous system (CNS) metastases.

2.3 Randomization and masking

Patients were randomized (1:1) to receive ramucirumab plus erlotinib (RAM + ERL) or placebo plus erlotinib (PL + ERL) via an interactive web-response system with a computer-generated random sequence. Patients were stratified by sex, geographical region (East Asia vs other), EGFR mutation type (Ex19del vs Ex21.L858R), and EGFR testing method (therascreen® or cobas® vs other polymerase chain reaction and sequencing-based methods). Patients, investigators, and all clinical study personnel were masked to the assigned treatment and will continue to be masked until after the final overall survival (OS) analysis.

2.4 Treatment protocol

Patients received intravenous ramucirumab 10 mg/kg once every 2 wk plus oral erlotinib 150 mg/d or intravenous placebo once every 2 wk plus oral erlotinib 150 mg/d. Treatment continued until radiographic progression (assessed by the investigator according to RECIST), unacceptable toxicity, noncompliance, patient withdrawal of consent, or investigator decision.

2.5 Assessments

Tumor response was assessed by computed tomography or magnetic resonance imaging every 6 wk from the first dose of study therapy up to 72 wk, then every 12 wk until disease progression or study discontinuation, and at the 30-d short-term follow-up visit. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. EGFR T790M mutation status was assessed in liquid biopsy samples at baseline and the 30-d follow-up visit using Guardant360 next-generation sequencing (Guardant Health).

2.6 Outcomes

The primary endpoint for the randomized phase III portion of RELAY was PFS (defined as the time from randomization to disease progression or death from any cause) as assessed by investigators according to RECIST. Secondary endpoints included objective response rate (ORR; percentage of patients achieving a complete response or partial response); disease control rate (DCR; percentage of patients achieving complete response, partial response, or stable disease); DoR (time from first documented response to the date of objective progression or the date of death, whichever occurred first; responders only); OS (time from randomization to date of death from any cause); and safety. Exploratory endpoints included biomarker analyses (EGFR T790M) and PFS2 (time from randomization to second disease progression or death from any cause, whichever occurred first).

2.7 Statistical analysis

The data cut-off date was January 23, 2019. Efficacy endpoints were assessed in the prespecified East Asian intention-to-treat (ITT) population, which included all randomly assigned patients from East Asian study sites. Safety endpoints were assessed in the East Asian safety population, which included all East Asian patients who received at least 1 dose of study treatment. For all time-to-event analyses (PFS, DoR, OS, PFS2), medians with 95% CIs were estimated using the Kaplan-Meier method, and HRs with 95% CIs were estimated using an unstratified Cox proportional hazard model. The ORR and DCR are reported along with the 95% CIs based on normal approximation. Treatment-emergent AEs (TEAEs), AEs of special interest (AESIs), and serious AEs (SAEs) were summarized as the number and percentage of patients reporting each event by treatment arm. The difference in T790M mutation frequency between arms was evaluated using Fisher exact test. Analyses were conducted using SAS version 9.4 (SAS Institute). RELAY was not powered for any prespecified subgroup, including the East Asian subgroup.

3 RESULTS

3.1 Patient disposition

Between January 28, 2016 and February 1, 2018, 449 patients were enrolled in the RELAY study (overall ITT population). The East Asian ITT population consisted of 336 (75% of global study population) patients (RAM + ERL: 166 patients; PL + ERL: 170 patients; Japan: 41 sites, 211 patients; Taiwan: 8 sites, 56 patients; South Korea: 10 sites, 54 patients; Hong Kong: 2 sites, 15 patients) (Figure S1). Two East Asian patients randomized to RAM + ERL did not receive any study treatment due to an AE or physician decision. Median duration of follow-up was 22.1 mo (minimum-maximum: 0.1-35.4). At the time of data cut-off, 42/166 patients (25.3%) in the RAM + ERL arm and 26/170 patients (15.3%) in the PL + ERL arm were still on study treatment. The most common reasons for discontinuation of all study treatment were progressive disease (RAM + ERL: 82/166 patients [49.4%]; PL + ERL: 113/170 patients [66.5%]) and AEs (RAM + ERL: 22/166 patients [13.3%]; PL + ERL: 22/170 patients [12.9%]).

3.2 Baseline demographics and clinical characteristics

Baseline patient and clinical characteristics of the East Asian ITT population were balanced between the 2 treatment arms and were reflective of an EGFR-mutated patient population (Table 1). All patients enrolled in East Asia were of Asian ethnicity.
3.3 | Efficacy

In the East Asian ITT population, PFS (investigator-assessed) was superior in the RAM + ERL arm compared with the PL + ERL arm (Figure 1). Median (95% CI) PFS was 19.4 (15.2-22.0) vs 12.5 (9.7-13.9) mo (unstratified HR [95% CI]: 0.692 [0.485-0.918]). Similar results were also seen in the prespecified investigator-assessed PFS results (unstratified HR [95% CI]: 0.636 [0.485-0.833]; P = .0009), and the 1-y PFS rate was 72.4% vs 52.2%. A sensitivity analysis of PFS by blinded, independent central review was consistent with the investigator-assessed PFS results (unstratified HR [95% CI]: 0.692 [0.485-0.918]). Similar results were also seen in the prespecified Asian race subgroup (also includes patients of Asian race enrolled outside East Asia) (N = 346) of the overall ITT population (unstratified HR [95% CI]: 0.638 [0.489-0.833]; P = .0009).

A PFS benefit for RAM + ERL vs PL + ERL was observed in most other prespecified subgroups, including sex and performance status (Figure 2). Analysis by EGFR mutation type showed improvements in PFS of similar magnitude for RAM + ERL vs PL + ERL in the Ex19del and Ex21.L858R subgroups (Figures 2 and 3). Median (95% CI) in the Ex19del subgroup was 19.2 (15.1-22.2) vs 12.4 (11.0-15.9) mo (unstratified HR [95% CI]: 0.629 [0.430-0.921]) and 19.4 (14.1-22.1) vs 12.5 (9.7-13.9) mo (unstratified HR [95% CI]: 0.644 [0.439-0.945]) in the Ex21.L858R subgroup for the RAM + ERL vs PL + ERL arms, respectively. There is currently no clear explanation for the difference in HRs between EGFR mutation testing method subgroups.

The ORR and DCR were similar between the RAM + ERL and PL + ERL arms (Table 2), as was the best percentage change from baseline in tumor size (Figure S2). In patients who responded, median DoR was longer in the RAM + ERL arm than in the PL + ERL arm (16.2 [13.8-19.8] vs 11.1 [9.7-12.5]; unstratified HR [95% CI]: 0.646 [0.481-0.868]; P = .0036) (Table 2).

At data cut-off, OS data were immature, with a censoring rate of 84.3% and 81.2% in the RAM + ERL and PL + ERL arms, respectively; the OS HR (95% CI) was 0.824 (0.491-1.383) (Table 2 and Figure S3). PFS2 data were also immature, with a censoring rate of 70.5% and 64.1% in the RAM + ERL and PL + ERL arms, respectively; the PFS2 HR (95% CI) was 0.771 (0.529-1.124) (Table 2 and Figure S4).

3.4 | Occurrence of CNS metastases

The CNS was a site of disease progression in 10 patients in the East Asian subset. CNS metastases were reported in 2 patients in the RAM + ERL arm and 8 patients in the PL + ERL arm.

3.5 | Post-progression EGFR T790M rates

As per the eligibility criteria, no patients had a known EGFR T790M mutation at baseline. Post-progression results were available for 95 patients in the East Asian subset whose disease had progressed and who had EGFR-activating mutation (Ex19del or Ex21.L858R) detected at the 30-d follow-up. In this group of patients, the proportion of patients with T790M mutation was similar between treatment arms (RAM + ERL, 15/35 patients, 43% [95% CI: 28-59]; PL + ERL, 30/60 patients, 50% [95% CI: 38-62]).

3.6 | Treatment exposure

In the RAM + ERL arm, 124/164 patients (75.6%) had a ramucirumab dose adjustment and 106/164 patients (64.6%) had an erlotinib dose adjustment. In the PL + ERL arm, 97/170 patients (57.1%) had a placebo dose adjustment and 97/170 patients (57.1%) had an erlotinib dose adjustment. Ramucirumab or placebo dose adjustments

### TABLE 1  Demographic and clinical characteristics of patients at baseline (East Asian ITT population)

| Characteristic | RAM + ERL (n = 166) | PL + ERL (n = 170) |
|---------------|-------------------|------------------|
| Age, y        |                   |                  |
| Median (min-max) | 65.0 (41-86) | 64.0 (35-83) |
| ≥65           | 91 (54.8)         | 82 (48.2)       |
| Gender        |                   |                  |
| Female        | 107 (64.5)        | 109 (64.1)      |
| Male          | 59 (35.5)         | 61 (35.9)       |
| Race          |                   |                  |
| Asian         | 166 (100)         | 170 (100)       |
| Smoking status|                   |                  |
| Ever          | 41 (24.7)         | 52 (30.6)       |
| Never         | 105 (63.3)        | 109 (64.1)      |
| Unknown or missing | 20 (12.0) | 9 (5.3)        |
| ECOG PS       |                   |                  |
| 0             | 86 (51.8)         | 91 (53.5)       |
| 1             | 80 (48.2)         | 79 (46.5)       |
| Disease stage at study entry |       |                  |
| Metastatic disease | 146 (88.0) | 146 (85.9)     |
| Recurrent metastatic disease | 20 (12.0) | 24 (14.1)     |
| EGFR mutation type |          |                  |
| Ex19del      | 84 (50.6)         | 84 (49.4)       |
| L858R        | 80 (48.2)         | 86 (50.6)       |
| EGFR testing method |          |                  |
| therascreen® or cobas® | 62 (37.3) | 67 (39.4)     |
| Other PCR and sequencing-based methods | 103 (62.0) | 103 (60.6) |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ERL, erlotinib; ITT, intention-to-treat; PCR, polymerase chain reaction; PL, placebo; RAM, ramucirumab.

Except where otherwise indicated, data are n (%).a

In the global ITT population, there were 346 patients in the Asian race subgroup (172 in the RAM + ERL arm and 174 in the PL + ERL arm).b

In the RAM + ERL arm, 1 patient was classified as Other and 1 patient was classified as Missing.c

In the RAM + ERL arm, 1 patient was classified as Missing.d
were mainly delays (RAM + ERL: 87.9% [109/124]; PL + ERL: 93.8% [91/97]), mostly due to an AE, most commonly blood bilirubin increased and alanine aminotransferase increased. Erlotinib dose adjustments were mainly omissions (RAM + ERL: 84.9% [90/106]; PL + ERL: 85.6% [83/97]) and/or reductions (RAM + ERL: 71.7% [76/106]; PL + ERL: 74.2% [72/97]); almost all dose adjustments were due to an AE, most commonly dermatitis acneiform.

Dose adjustments had minimal effect on dose intensity, which was >90% for all drugs. In the RAM + ERL arm, median (minimum–maximum) duration of exposure (censored analysis excluding 42 patients still on treatment) to ramucirumab was 11.7 (0.5-33.8) mo and to erlotinib was 15.1 (<0.1-33.8) mo. In the PL + ERL arm, median (minimum–maximum) duration of exposure (censored analysis excluding 26 patients still on treatment) to placebo was 10.4 (0.5-35.4) mo and to erlotinib was 11.3 (0.8-35.5) mo.

### 3.7 | Post-discontinuation therapy

Per the protocol, all study treatment had to be discontinued for RECIST progression. This differs from clinical practice and guidelines, in which treatment after RECIST-defined progression...
is allowed if there is continued benefit as judged by the treating physician. In RELAY, any subsequent anticancer therapy after discontinuation of all study treatment (regardless of reason for discontinuation) was at the investigator’s discretion and therefore could include erlotinib or another EGFR TKI if considered beneficial to the patient. Of those patients who discontinued all study treatment, 94/122 (77.0%) patients in the RAM+ERL arm and 122/144 (84.7%) patients in the PL+ERL arm received at least 1 subsequent line of systemic anticancer therapy (ie, second-line treatment), of which an EGFR TKI, particularly erlotinib (56.4% and 37.7% for RAM+ERL and PL+ERL, respectively) and osimertinib (13.8% and 18.0%), was the most common (Table S1). Chemotherapy was received by 20.2% and 25.4% of patients in the RAM+ERL and PL+ERL arms, respectively. A second subsequent line of therapy (ie, third-line treatment) was received by 56 patients in the RAM+ERL arm and 68 patients in the PL+ERL arm (Table S1), of which chemotherapy was the most frequently used treatment (44.6% and 60.3% of patients in the RAM+ERL and PL+ERL arms, respectively), and osimertinib the most frequently used EGFR TKI (39.3% and 25.0% of patients in the RAM+ERL and PL+ERL arms, respectively). Overall, osimertinib was used as any subsequent line of therapy in 41/94 (43.6%) and 43/122 (35.2%) patients in the RAM+ERL and PL+ERL arms, respectively.

3.8 | Safety

All patients in the East Asian safety population reported at least 1 TEAE; the most common TEAEs of any grade in the RAM+ERL and PL+ERL arms were acneiform dermatitis (78.7% vs 77.6%), diarrhea (68.3% vs 69.4%), and paronychia (61.0% vs 58.8%) (Table 3). Grade ≥ 3 TEAEs were more common in the RAM+ERL arm (70.7%) than in the PL+ERL arm (49.4%); those with a ≥ 5% difference between arms included hypertension (35/164 patients [21.3%] vs 8/170 patients [4.7%]) and acneiform dermatitis (30/164 patients [18.3%] vs 15/170 patients [8.8%]) (Table 3). Grade 3 hypertension was the largest contributor to grade ≥ 3 TEAEs in the RAM+ERL arm.

Any-grade AESIs reported more commonly in the RAM+ERL arm than in the PL+ERL arm were bleeding/hemorrhage events (any grade: 55.5% vs 27.1%; mostly grade 1-2 events; mainly epistaxis), hypertension (any grade: 42.7% vs 11.8%; grade 3: 21.3% vs 4.7%; no grade 4-5 events reported), and proteinuria (any grade: 38.4% vs 7.6%) (Table 3).

Any-grade interstitial lung disease (ILD) events (including pneumonitis) were reported by 3/164 patients (1.8%) in the RAM+ERL arm (grade 3: 1/164 patients [0.6%]) and 6/170 patients (3.5%) in the PL+ERL arm (grade 3: 3/170 patients [1.8%]) (Table 3); no grade 4 ILD events were reported. One patient in the PL+ERL arm had a fatal event of ILD more than 30 d after discontinuing study treatment.
The proportion of patients with treatment-emergent SAEs was higher in the RAM + ERL arm than in the PL + ERL arm (51/164 patients [31.1%] vs 39/170 patients [22.9%]). Treatment-related SAEs were reported in 26/164 patients (15.9%) in the RAM + ERL arm and in 21/170 patients (12.4%) in the PL + ERL arm. There was 1 death on study treatment due to an AE (RAM + ERL arm; influenza encephalitis, after a single dose of RAM, which was not considered related to study treatment).

### DISCUSSION

The global RELAY study showed superior PFS for RAM + ERL vs PL + ERL in patients with previously untreated metastatic EGFR-mutated NSCLC (median PFS: 19.4 vs 12.4 mo; HR [95% CI]: 0.591 [0.461-0.760]).18 The patient characteristics of the East Asian subset are similar to what others have found in the same population, with a higher prevalence of Ex21.L858R mutations and never-smokers than Caucasian populations.5,21 In this prespecified East Asian subset analysis of RELAY, RAM + ERL demonstrated clinically meaningful22 and significant improvements in efficacy over PL + ERL (median PFS: 19.4 vs 12.5 mo; HR [95% CI]: 0.636 [0.485-0.833]). The Kaplan-Meier curves showed an early separation, which was maintained throughout follow-up. The PFS benefit was consistent with the prespecified analysis by race in the overall study population and across prespecified subgroups within the East Asian subset. Further, the PFS benefit was accompanied by a consistent benefit for RAM + ERL vs PL + ERL in secondary, exploratory, and subgroup analyses (DoR, PFS2, PFS by EGFR mutation type) and a manageable safety profile. These results support the RELAY regimen as an effective and safe treatment option in the East Asian population.

The PFS benefit of RAM + ERL in the East Asian RELAY subset was in line with that observed in previous trials of the anti-VEGF monoclonal antibody bevacizumab plus erlotinib vs erlotinib alone conducted in Japanese patients; specifically, the phase II, open-label JO25567 trial (median [95% CI] PFS: 16.0 [13.9-18.1] vs 9.7 [5.7-11.1] mo, HR [95% CI]: 0.54 [0.36-0.79]; P = .0015)16 and the phase III, open-label NEJ026 trial (median [95% CI] PFS: 16.9 [14.2-21.0] vs 13.3 [11.1-15.3] mo, HR [95% CI]: 0.605 [0.417-0.877]; P = .016),17 further supports that dual EGFR/VEGF inhibition is a viable strategy to improve patient outcomes. A PFS benefit relative to first-generation EGFR TKIs in Asian patients has also been demonstrated for dacomitinib (ARCHER 1050 Asian subgroup: HR [95% CI]: 0.51 [0.39-0.66])23 and osimertinib (FLAURA Asian subgroup: HR [95% CI]: 0.55 [0.42-0.72]).24 In contrast, the OS benefit seen with first-line osimertinib in the overall FLAURA population (HR [95.05% CI]: 0.80 [0.64-1.00]) was not seen in the Asian (HR [95% CI]: 1.00 [0.75-1.32]) or EGFR Ex21.L858R (HR [95% CI]: 1.00 [0.71-1.40]) subgroups.25

Although Ex19del and Ex21.L858R are both associated with response to EGFR TKIs, the PFS benefit associated with Ex21.L858R is generally smaller than that observed for Ex19del.6 In RELAY, median PFS for patients receiving RAM + ERL in the Ex21.L858R and Ex19del subgroups was similar in both the East Asian subset (19.4 vs 19.2 mo) and the overall study population (19.4 vs 19.6 mo).18 Of note, the median PFS of 19.4 mo reported for the Ex21.L858R subgroup in the East Asian subset and the overall study population18 is, to our knowledge, the longest median PFS reported so far for patients with Ex21.L858R in the first-line setting. Median PFS values ranging from 7.1 to 14.4 mo have been reported in the Ex21.L858R patient subgroup in first-line studies of EGFR TKI monotherapy (FLAURA,24 ARCHER 1050,23 EURTAC25) and from 13.9 to 17.4 mo in combination with bevacizumab (JO2556714 and NEJ02617).

As for the overall RELAY study population,18 there was a consistent clinical benefit in the East Asian subset for RAM + ERL vs PL + ERL in the secondary and exploratory analyses. The ORR was similar between the 2 treatment arms, however the median DoR was longer with RAM + ERL than with PL + ERL, which contributed...
to the prolonged PFS in the RAM + ERL arm. Although a limitation of RELAY is that OS data were immature at data cut-off, the available results suggest that the addition of ramucirumab to erlotinib does not have a detrimental effect on OS in East Asian patients with EGFR-mutated NSCLC. When OS data are immature, PFS2 is recommended by the European Medicines Agency as a surrogate endpoint for OS. As it was defined in RELAY, PFS2 encompasses PFS on study treatment and on the subsequent therapy and, therefore, measures the continued impact of first-line therapy through second progression. Although still immature, the preliminary PFS2 data in the RELAY East Asian subset suggest that the RAM + ERL treatment effect was preserved after discontinuation of study treatment and a benefit was maintained through second disease progression.

The safety profile of RAM + ERL in the East Asian subset was consistent with that observed for the overall RELAY study population with respect to the type and severity of reported AEs and the rates of dose reductions and omissions/delays. As anticipated, class-related effects of VEGF/VEGF receptor antagonists, such as hypertension, proteinuria, and bleeding events, were reported more frequently in the RAM + ERL arm than in the PL + ERL arm. Most proteinuria and bleeding events were grade 1 or 2 in severity. Hypertension was the most commonly reported grade 3 TEAE in the RAM + ERL arm, reported by 21.3% of patients; no grade 4 or 5 hypertension events were reported. Similarly, in the NEJ026 trial, grade 3 hypertension was reported in 23% of patients receiving bevacizumab and erlotinib. Indeed, hypertension is a well-known class effect of VEGF/VEGF receptor antagonists and is well managed in clinical practice. Any-grade diarrhea and acneiform dermatitis, both associated with EGFR TKI treatment, were reported in similar percentages of patients in the RAM + ERL and PL + ERL arms in the East Asian subset. As observed in the overall RELAY study population, the incidence of some erlotinib-associated TEAEs was

### Table 3: TEAEs occurring in ≥40% of patients in the RAM + ERL arm and AESIs for ramucirumab (East Asian safety population)

| TEAEs, n (%) | RAM + ERL (n = 164) | PL + ERL (n = 170) |
|--------------|---------------------|---------------------|
|              | Any Grade | Grade ≥ 3 | Any Grade | Grade ≥ 3 |
| ≥1 TEAE      | 164 (100) | 116 (70.7) | 170 (100) | 84 (49.4) |
| Acneiform dermatitis | 129 (78.7) | 30 (18.3) | 132 (77.6) | 15 (8.8) |
| Diarrhea     | 112 (68.3) | 9 (5.5) | 118 (69.4) | 2 (1.2) |
| Paronychia   | 100 (61.0) | 8 (4.9) | 100 (58.8) | 6 (3.5) |
| Increased ALT| 76 (46.3) | 15 (9.1) | 60 (35.3) | 16 (9.4) |
| Stomatitis   | 75 (45.7) | 2 (1.2) | 62 (36.5) | 2 (1.2) |
| Increased AST| 73 (44.5) | 7 (4.3) | 51 (30.0) | 8 (4.7) |
| Hypertension | 70 (42.7) | 35 (21.3) | 20 (11.8) | 8 (4.7) |

### AESIs, n (%)

| AESIs | RAM + ERL (n = 164) | PL + ERL (n = 170) |
|-------|---------------------|---------------------|
|       | Any Grade | Grade ≥ 3 | Any Grade | Grade ≥ 3 |
| Bleeding/hemorrhage | 91 (55.5) | 3 (1.8) | 46 (27.1) | 2 (1.2) |
| Epistaxis | 58 (35.4) | 0 (0) | 22 (12.9) | 0 (0) |
| GI hemorrhage | 17 (10.4) | 3 (1.8) | 4 (2.4) | 0 (0) |
| Pulmonary hemorrhage | 10 (6.1) | 0 (0) | 3 (1.8) | 0 (0) |
| Hypertension | 70 (42.7) | 35 (21.3) | 20 (11.8) | 8 (4.7) |
| Proteinuria | 63 (38.4) | 4 (2.4) | 13 (7.6) | 0 (0) |
| Liver failure/liver injury | 109 (66.5) | 22 (13.4) | 103 (60.6) | 24 (14.1) |
| Increased ALT | 76 (46.3) | 15 (9.1) | 60 (35.3) | 16 (9.4) |
| Increased blood bilirubin | 55 (33.5) | 2 (1.2) | 60 (35.3) | 0 (0) |
| Infusion-related reactions | 3 (1.8) | 0 (0) | 1 (0.6) | 0 (0) |

Other TEAE of interest, n (%)

| ILD | 3 (1.8) | 1 (0.6) | 6 (3.5) | 3 (1.8) |

Note: Includes adverse events with onset date on or after date of first dose up to and including 30 d follow-up after discontinuation of study treatment.

Abbreviations: AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERL, erlotinib; GI, gastrointestinal; ILD, interstitial lung disease; PL, placebo; RAM, ramucirumab; TEAE, treatment-emergent adverse event.

ILD events included pneumonitis.
higher in the RAM + ERL arm than in the PL + ERL arm, including grade ≥ 3 diarrhea and acneiform dermatitis, low-grade stomatitis, and increases in alanine and aspartate aminotransferases. ILD is a well known AE related to EGFR TKIs more frequently reported in Asian (particularly Japanese) patients than in non-Asian patients. In the RELAY East Asian subset, the occurrence of ILD was lower in the RAM + ERL arm than in the PL + ERL arm (1.8% vs 3.5%), consistent with the global RELAY population (1% vs 2%). In NEJ026, no ILD events were reported in the bevacizumab plus erlotinib arm compared with 4% of patients in the erlotinib monotherapy arm. In the FLAURA trial, ILD was reported in 4% of patients in the osimertinib arm vs 2% of patients in the standard-of-care EGFR TKI arm, and similar results were seen in the FLAURA Asian subset (6% vs 2%)

Acquired resistance to EGFR TKIs limits their long-term efficacy, with the most common form of resistance being the EGFR T790M mutation, which occurs in 30%-60% of patients. In the current analysis, the EGFR T790M mutation rate at progression was similar between treatment arms (43% and 50% of patients in the RAM + ERL and PL + ERL arms, respectively), suggesting that the addition of ramucirumab to erlotinib does not alter the T790M resistance mechanism pathway in East Asian patients with EGFR-mutated metastatic NSCLC. Thus, subsequent treatment with an agent that targets the EGFR T790M mutation, such as osimertinib, could further delay disease progression and time to chemotherapy for the considerable proportion of patients who acquire the EGFR T790M mutation. Indeed, osimertinib was used as post-discontinuation therapy across all subsequent lines of therapy in 43.6% of patients in the RAM + ERL arm and 35.2% of patients in the PL + ERL arm. Osimertinib only approved for patients with metastatic EGFR T790M mutation-positive NSCLC whose disease had progressed on or after EGFR TKI treatment after the RELAY study was initiated. In addition, because the emergence of T790M appears to be delayed in patients treated with RAM + ERL, these patients may have been less affected by the delay in access to osimertinib. Regardless, the rates of subsequent osimertinib use may be ultimately underestimated for these reasons. It is also important to recognize that the T790M mutation rates reported here were assessed in a subset of patients as part of an exploratory biomarker analysis, and that clinical decisions about subsequent therapies were based on local T790M testing results, not on the central testing results reported here. Overall, optimal treatment sequencing will become of critical importance to further improve patient outcomes.

Our results are based on the subset of East Asian patients enrolled in RELAY, a phase III trial with a robust, double-blind, placebo-controlled study design. However, the current analysis was not powered to show differences between ramucirumab and placebo in the East Asian subset and, therefore, results need to be interpreted with caution. Further investigation is needed to make definitive conclusions regarding the efficacy of RAM + ERL in East Asian patients with EGFR-mutated metastatic NSCLC.

At the time RELAY was initiated, erlotinib was selected as it was the only EGFR TKI with global regulatory approval, and no data were available to support superiority of any specific EGFR TKI. Studies of ramucirumab in combination with other EGFR TKIs, specifically, gefitinib (Part C of the RELAY study) and osimertinib (NCT02789345 and NCT03909334), are now ongoing.

In conclusion, the efficacy and safety outcomes for RAM + ERL in the RELAY East Asian subset were consistent with those for the overall RELAY study population. The RAM + ERL treatment regimen demonstrated superior PFS compared with PL + ERL in the East Asian subset, with a safety profile that was manageable and consistent with the established safety profiles of ramucirumab and erlotinib in EGFR-mutated metastatic NSCLC. The results of this subgroup analysis indicate that ramucirumab in combination with erlotinib is an effective, safe, and viable option for the first-line treatment of East Asian patients with EGFR-mutated metastatic NSCLC.

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Eli Lilly and Company was involved in the study design, data collection, data analysis, and preparation of the manuscript.

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CONFICT OF INTEREST
M. Nishio has received lecture fees, honoraria, or other fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo Healthcare, Eli Lilly and Company, Merck Serono, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, and Taiho Pharmaceutical, and research funds from Astellas, AstraZeneca, Bristol Myers Squibb, Chugai Pharmaceutical, Eli Lilly and Company, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, and Taiho Pharmaceutical. T. Seto is an employee of Precision Medicine Asia and has received lecture fees, honoraria, or other fees from AstraZeneca, Chugai Pharmaceutical, Eli Lilly Japan, Merck Sharp & Dohme, Pfizer Japan, and Taiho Pharmaceutical. C.-H. Chiu has no conflicts of interest to declare. K. Yoh has received lecture fees, honoraria, or other fees from Chugai Pharmaceutical and Eli Lilly and Company, and research funds from Eli Lilly and Company. F. Imamura has received lecture fees, honoraria, or other fees from AstraZeneca, and research funds from AstraZeneca, Boehringer

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DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected dur-

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APPENDIX I

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| Cicin                  | Irfan                   | Trakya University Faculty of Medicine | Balkan Yerleskesi | EDIRNE | | 22770 | Turkey |
Six sites screened but did not randomize patients.