Received: 9 July 2020 | Revised: 7 September 2020 | Accepted: 12 September 2020

DOI: 10.1111/cas.14655

ORIGINAL ARTICLE

Cancer Science WILEY

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

Makoto Nishio[1] | Takashi Seto[2] | Martin Reck[3] | Edward B. Garon[4] | Chao-Hua Chiu[5] | Kiyotaka Yoh[6] | Fumio Imamura[7] | Keunchil Park[8] | Jin-Yuan Shih[9] | Carla Visseren-Grul[10] | Bente Frimodt-Moller[11] | Annamaria Zimmermann[12] | Gosuke Homma[13] | Sotaro Enatsu[13] | Kazuhiko Nakagawa[14] | RELAY Study Investigators

[1]The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

[2]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

[3]LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany

[4]David Geffen School of Medicine at UCLA/TRIO-US Network, Los Angeles, CA, USA

[5]Taipei Veterans General Hospital, Taipei, Taiwan

[6]National Cancer Center Hospital East, Kashiwa, Japan

[7]Osaka International Cancer Institute, Osaka, Japan

[8]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[9]National Taiwan University Hospital, Taipei, Taiwan

[10]Eli Lilly and Company, Utrecht, The Netherlands

[11]Eli Lilly and Company, Copenhagen, Denmark

[12]Eli Lilly and Company, Indianapolis, IN, USA

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, *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; PD, progressive disease; 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.

ClinicalTrials.gov: NCT02411448.

[13]Eli Lilly Japan KK, Kobe, Japan

[14]Kindai University Faculty of Medicine, Osaka, Japan

Correspondence
Makoto Nishio, Department of Thoracic Medical Oncology, The Cancer Institute Hospital of JFCR, 3 Chome-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan.
Email: mnishio@jfcr.or.jp

Funding information
Eli Lilly and Company.

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.[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.[2] EGFR tyrosine kinase inhibitor (TKI) therapy is the first-line standard of care in patients with advanced NSCLC with activating *EGFR* mutations,[3,4] and many of the landmark trials in the development of EGFR TKIs were conducted in Asian patients.[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.[5,6] Although the presence of activating *EGFR* mutations predicts sensitivity to EGFR TKIs, the treatment benefit may differ depending on *EGFR* mutation type.[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.[7] Regardless of initial response, acquired resistance to EGFR TKIs results in treatment failure.[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.[9-12] The mechanisms of resistance to third-generation EGFR TKIs, such as osimertinib, are heterogeneous and difficult to target.[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.[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]; $P < .0001$).[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).[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.[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.[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.[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[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

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 (11.1-13.9) mo (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 [0.522-0.918]). 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).

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

Characteristic[a]	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[b]	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[c]		
Ex19del	84 (50.6)	84 (49.4)
L858R	80 (48.2)	86 (50.6)
EGFR testing method[d]		
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]

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

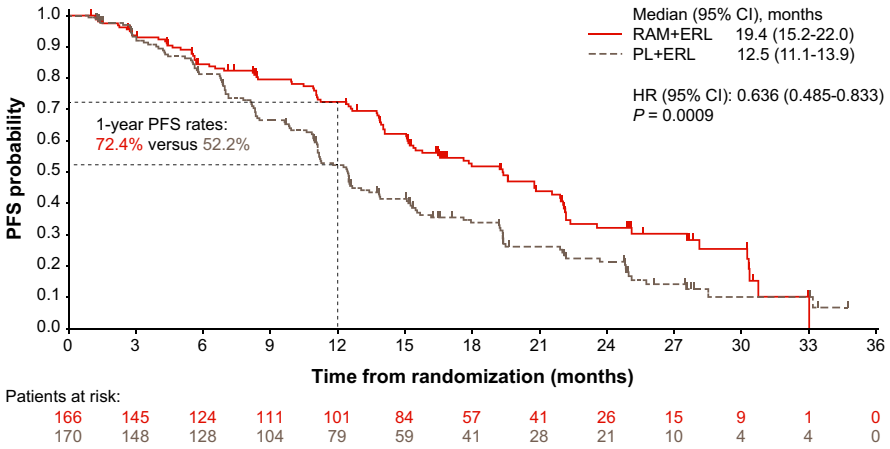

FIGURE 1 Kaplan-Meier plot of progression-free survival (PFS; investigator-assessed) in the RELAY East Asian subset. For the analysis of PFS, data for patients who had not had a progression event or had not died at the time of the analysis were censored at the time of their last evaluable assessment (according to the Response Evaluation Criteria in Solid Tumors). CI, confidence interval; ERL, erlotinib; HR, hazard ratio; PL, placebo; RAM, ramucirumab

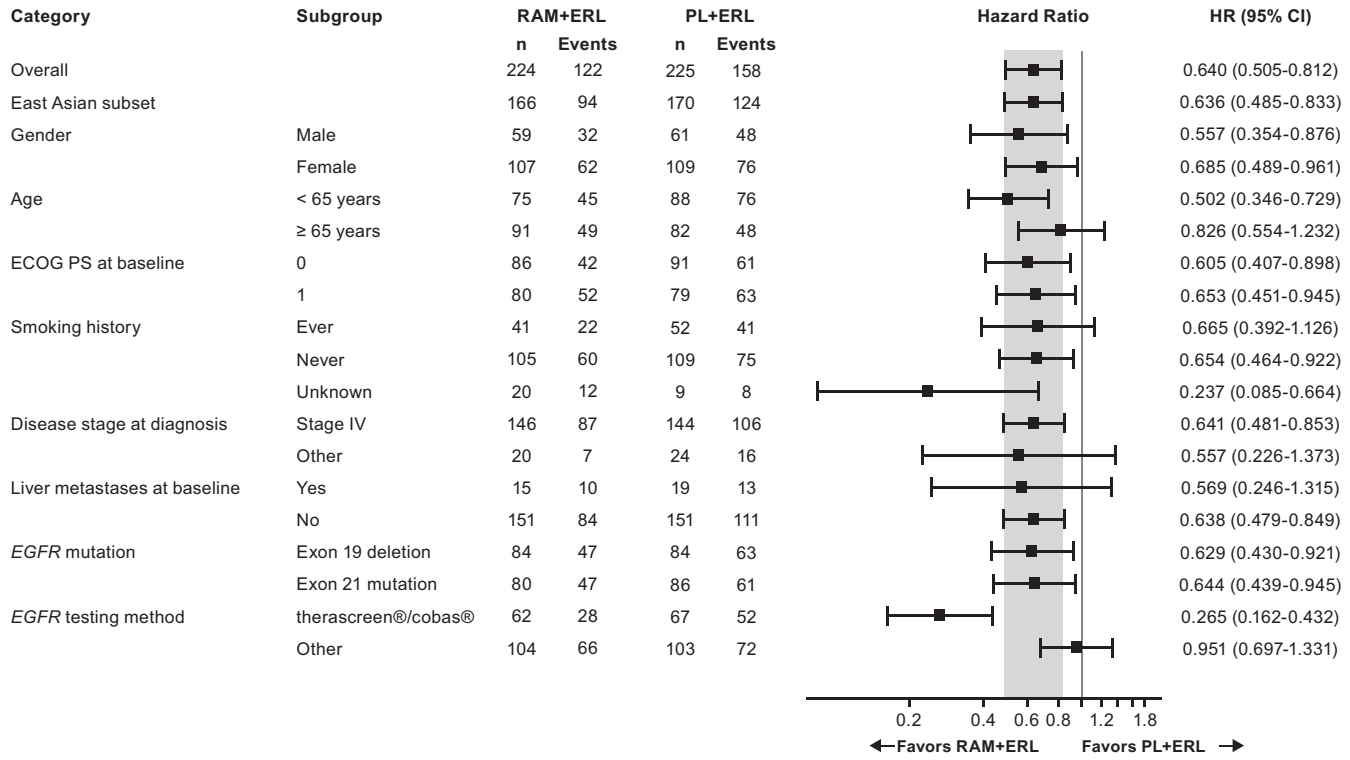

FIGURE 2 Subgroup analysis of progression-free survival (investigator-assessed). The gray column is the width of the 95% confidence intervals (CIs) in the East Asian intention-to-treat population. All hazard ratios (HRs) are from unstratified analyses. ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; ERL, erlotinib; PL, placebo; RAM, ramucirumab

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 (interquartile range) relative dose intensity of ramucirumab was 94.1% (85.7-99.6) and of erlotinib was 92.0% (66.6-100.0). In the PL + ERL arm, median (interquartile range) relative dose intensity of placebo was 97.7% (90.8-110.6) and of erlotinib was 96.1% (68.1-100.0). 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

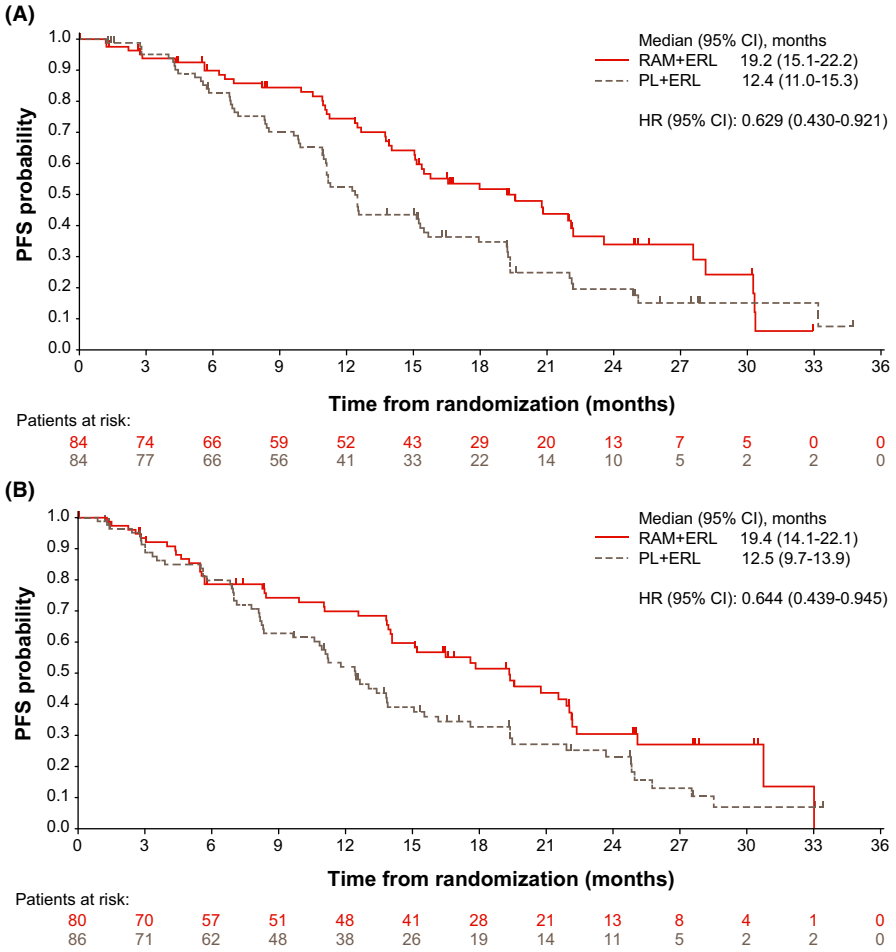

FIGURE 3 Kaplan-Meier plot of progression-free survival (PFS; investigator-assessed) in the RELAY East Asian subset in patients with (A) the *EGFR* exon 19 deletion mutation at baseline and (B) the *EGFR* exon 21 point mutation at baseline. For the analysis of PFS, data for patients who had not had a progression event or had not died at the time of the analysis were censored at the time of their last assessment (according to the Response Evaluation Criteria in Solid Tumors) that could be evaluated. CI, confidence interval; ERL, erlotinib; HR, hazard ratio; PL, placebo; RAM, ramucirumab

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.

TABLE 2 Secondary and exploratory efficacy endpoints (East Asian ITT population)

Parameter	RAM + ERL (n = 166)	PL + ERL (n = 170)
Best overall response, n (%)		
Complete response	1 (0.6)	0
Partial response	127 (76.5)	126 (74.1)
Stable disease	28 (16.9)	37 (21.8)
Progressive disease	3 (1.8)	4 (2.4)
Not evaluable	7 (4.2)	3 (1.8)
ORR, n	128	126
% (95% CI)	77.1 (70.7-83.5)	74.1 (67.5-80.7)
DCR, n	156	163
% (95% CI)	94.0 (90.4-97.6)	95.9 (92.9-98.9)
Duration of response[a]		
Median (95% CI), mo	16.2 (13.8-19.8)	11.1 (9.7-12.5)
Unstratified HR (95% CI)	0.646 (0.481-0.868)	
Patients with continued response,[a] % (95% CI)		
At 12 mo	65.7 (56.5-73.4)	44.2 (35.2-52.8)
At 18 mo	48.7 (39.2-57.6)	24.6 (17.0-32.9)
Interim OS		
Events, n	26	32
Censoring rate, %	84.3	81.2
Unstratified HR (95% CI)	0.824 (0.491-1.383)	
Survival rate, % (95% CI)		
At 12 mo	94.4 (89.4-97.0)	95.2 (90.7-97.6)
At 18 mo	87.2 (80.6-91.6)	90.0 (84.1-93.7)
PFS2		
Events, n	49	61
Censoring rate, %	70.5	64.1
Unstratified HR (95% CI)	0.771 (0.529-1.124)	

Abbreviations: CI, confidence interval; DCR, disease control rate; ERL, erlotinib; HR, hazard ratio; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS2, time to second disease progression; PL, placebo; RAM, ramucirumab.

[a]In patients who responded (RAM + ERL: n = 128; PL + ERL: n = 126).

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).

4 | 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 meaningful[22] 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] and 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 population[18] 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 subpopulation in first-line studies of EGFR TKI monotherapy (FLAURA,[24] ARCHER 1050,[23] EURTAC[26]) and from 13.9 to 17.4 mo in combination with bevacizumab (JO25567[16] and NEJ026[17]).

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

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

	RAM + ERL (n = 164)		PL + ERL (n = 170)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
TEAEs, n (%)				
≥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 (%)				
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[a]	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.[a]

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.[27] 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.[18] 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.[17] Indeed, hypertension is a well-known class effect of VEGF/VEGF receptor antagonists and is well managed in clinical practice.[28,29] Any-grade diarrhea and acneiform dermatitis, both associated with EGFR TKI treatment,[30,31] 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,[18] the incidence of some erlotinib-associated TEAEs was

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.[32] In the RELAY East Asian subset, the incidence 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%).[18] In NEJ026, no ILD events were reported in the bevacizumab plus erlotinib arm compared with 4% of patients in the erlotinib monotherapy arm.[17] 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,[24] and similar results were seen in the FLAURA Asian subset (6% vs 2%).[33]

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.[9-12] 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,[34] 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 was 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,[18] 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.

ACKNOWLEDGMENTS

This study was sponsored by Eli Lilly and Company, manufacturer/licensee of ramucirumab. Medical writing assistance was provided by Rebecca Lew, PhD, CMPP, and Tania Dickson, PhD, CMPP, of ProScribe – Envision Pharma Group, and was funded by Eli Lilly Japan KK ProScribe's services complied with international guidelines for Good Publication Practice (GPP3).

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

The authors would like to thank all study participants, and Rebecca R. Hozak (Eli Lilly and Company) for *EGFR* T790M mutation analysis.

CONFLICT 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, and research funds from AbbVie, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, Kissei Pharmaceutical, LOXO Oncology, Merck Sharp & Dohme, Nippon Boehringer Ingelheim, Novartis, Pfizer Japan, and Takeda Pharmaceutical. M. Reck has no conflicts of interest to declare. E. B. Garon has received lecture fees, honoraria, or other fees from Novartis, and research funds from AstraZeneca, Bristol Myers Squibb, Eli Lilly and Company, EMD Serono, Genentech, Iovance, Merck, Mirati, Neon, and Novartis. 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

Ingelheim, Bristol Myers Squibb, and Chugai Pharmaceutical. K. Park has no conflicts of interest to declare. J.-Y. Shih has no conflicts of interest to declare. C. Visseren-Grul, B. Frimodt-Moller, A. Zimmermann, G. Homma, and S. Enatsu are employees and minor shareholders of Eli Lilly and Company. K. Nakagawa has received lecture fees, honoraria, or other fees from Astellas, AstraZeneca, Eli Lilly Japan, Kyorin Pharmaceutical, Merck Sharp & Dohme, Nippon Boehringer Ingelheim, Novartis, Ono Pharmaceutical, and Pfizer Japan, and research funds from A2 Healthcare Corporation, AbbVie, Astellas, AstraZeneca, Bristol Myers Squibb, Chugai Pharmaceutical, CMIC Shift Zero, Daiichi Sankyo, Eisai, Eli Lilly Japan, ICON Japan, inVentiv Health Japan, IQVIA Services Japan, Kyowa Hakko Kirin, Merck Sharp & Dohme, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Pfizer Japan, SymBio Pharmaceuticals Limited, Syneos Health, Takeda Pharmaceutical, and Taiho Pharmaceutical.

DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 mo after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data 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, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

ORCID

Makoto Nishio https://orcid.org/0000-0003-4969-4165
Jin-Yuan Shih https://orcid.org/0000-0002-2854-5067

REFERENCES

1. World Health Organization. *GLOBOCAN 2018. Cancer Fact Sheets: Eastern Asia*. Geneva, Switzerland: World Health Organization; 2018. http://gco.iarc.fr/today/data/factsheets/populations/906-eastern-asia-fact-sheets.pdf. Accessed December 10, 2019.
2. Hsu WH, Yang JCH, Mok TS, Loong HH. Overview of current systemic management of EGFR-mutant NSCLC. *Ann Oncol*. 2018;29:i3-i9.
3. Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35:3484-3515.
4. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30:863-870.
5. Graham RP, Treece AL, Lindeman NI, et al. Worldwide frequency of commonly detected *EGFR* mutations. *Arch Pathol Lab Med*. 2018;142:163-167.
6. Sheng M, Wang F, Zhao Y, et al. Comparison of clinical outcomes of patients with non-small-cell lung cancer harbouring epidermal growth factor receptor exon 19 or exon 21 mutations after tyrosine kinase inhibitors treatment: a meta-analysis. *Eur J Clin Pharmacol*. 2016;72:1-11.
7. Gibson AJW, D'Silva A, Elegbede AA, et al. Impact of Asian ethnicity on outcome in metastatic EGFR-mutant non-small cell lung cancer. *Asia Pac J Clin Oncol*. 2019;15:343-352.
8. Wu SG, Shih JY. Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer. *Mol Cancer*. 2018;17:38.
9. Oxnard GR, Arcila ME, Sima CS, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res*. 2011;17:1616-1622.
10. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19:2240-2247.
11. Mayo-de-Las-Casas C, Jordana-Ariza N, Garzón-Ibañez M, et al. Large scale, prospective screening of EGFR mutations in the blood of advanced NSCLC patients to guide treatment decisions. *Ann Oncol*. 2017;28:2248-2255.
12. Seto T, Nogami N, Yamamoto N, et al. Real-world *EGFR* T790M testing in advanced non-small-cell lung cancer: a prospective observational study in Japan. *Oncol Ther*. 2018;6:203-215.
13. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121:725-737.
14. Byers LA, Heymach JV. Dual targeting of the vascular endothelial growth factor and epidermal growth factor receptor pathways: rationale and clinical applications for non-small-cell lung cancer. *Clin Lung Cancer*. 2007;8:S79-S85.
15. Naumov GN, Nilsson MB, Cascone T, et al. Combined vascular endothelial growth factor receptor and epidermal growth factor receptor (EGFR) blockade inhibits tumor growth in xenograft models of EGFR inhibitor resistance. *Clin Cancer Res*. 2009;15:3484-3494.
16. Seto T, Kato T, Nishio M, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol*. 2014;15:1236-1244.
17. Saito H, Fukuhara T, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol*. 2019;20:625-635.
18. Nakagawa K, Garon EB, Seto T, et al. 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. *Lancet Oncol*. 2019;20:1655-1669.
19. National Comprehensive Cancer Network. *Non-small Cell Lung Cancer*. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2020. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed March 12, 2020.
20. Edge S, Byrd DR, Compton CC, Fritz AG, Greene F, Trotti A. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer-Verlag; 2010.
21. Zhou W, Christiani DC. East meets West: ethnic differences in epidemiology and clinical behaviors of lung cancer between East Asians and Caucasians. *Chin J Cancer*. 2011;30:287-292.
22. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014;32:1277-1280.
23. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:1454-1466.

24. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113-125.
25. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2020;382:41-50.
26. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239-246.
27. European Medicines Agency. *Guideline on the evaluation of anticancer medicinal products in man*. EMA/CHMP/205/95 Rev. 5. November 20. Amsterdam, The Netherlands: European Medicines Agency; 2017. https://www.ema.europa.eu/en/evaluation-anticancer-medicinal-products-man. Accessed December 8, 2019.
28. Wasserstrum Y, Kornowski R, Raanani P, Leader A, Pasvolsky O, Iakobishvili Z. Hypertension in cancer patients treated with anti-angiogenic based regimens. *Cardio-Oncology*. 2015;1:6.
29. Pandey AK, Singhi EK, Arroyo JP, et al. Mechanisms of VEGF (vascular endothelial growth factor) inhibitor-associated hypertension and vascular disease. *Hypertension*. 2018;71:e1-e8.
30. Li J, Gu J. Diarrhea with epidermal growth factor receptor tyrosine kinase inhibitors in cancer patients: a meta-analysis of randomized controlled trials. *Crit Rev Oncol Hematol*. 2019;134:31-38.
31. Fabbrocini G, Panariello L, Caro G, Cacciapuoti S. Acneiform rash induced by EGFR inhibitors: review of the literature and new insights. *Skin Appendage Disord*. 2015;1:31-37.
32. Yoneda KY, Hardin KA, Gandara DR, Shelton DK. Interstitial lung disease associated with epidermal growth factor receptor tyrosine kinase inhibitor therapy in non-small-cell lung carcinoma. *Clin Lung Cancer*. 2006;8:S31-S35.
33. Cho BC, Chewaskulyong B, Lee KH, et al. Osimertinib versus standard of care EGFR TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA Asian subset. *J Thorac Oncol*. 2019;14:99-106.
34. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629-640.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Nishio M, Seto T, Reck M, et al; RELAY Study Investigators. Ramucirumab or placebo plus erlotinib in *EGFR*-mutated, metastatic non-small-cell lung cancer: East Asian subset of RELAY. *Cancer Sci* 2020;111:4510–4525. https://doi.org/10.1111/cas.14655

APPENDIX I

List of contributors (investigators who randomized at least 1 patient or screened for phase III [Part B])

Investigator last name	Investigator first name	Institution	Address	City	State/province	Postal code	Country
East Asia							
Takahashi	Toshiaki	Shizuoka Cancer Center	1007 Shimonagakubo Nagaizumi-Cho	Sunto-Gun	Shizuoka	411-8777	Japan
Nakagawa	Kazuhiko	Kindai University Hospital	377-2 Ohno-Higashi	Osaka Sayama-shi	Osaka	589-8511	Japan
Nishio	Makoto	The Cancer Institute Hospital of JFCR	3-8-31 Ariake	Koto-ku	Tokyo	135-8550	Japan
Yoh	Kiyotaka	National Cancer Center Hospital East	6-5-1 Kashiwanoha	Kashiwa	Chiba	277-8577	Japan
Seto	Takashi	Kyushu Cancer Center	3-1-1 Notame Minami-Ku	Fukuoka	Fukuoka	811-1395	Japan
Imamura	Fumio	Osaka International Cancer Institute	3-1-69 Otemae Chuou-ku	Osaka	Osaka	541-8567	Japan
Kumagai	Toru	Osaka International Cancer Institute	3-1-69 Otemae Chuou-ku	Osaka	Osaka	541-8567	Japan
Hotta	Katsuyuki	Okayama University Hospital	2-5-1 Shikata-Cho, Kita-ku	Okayama	Okayama	700-8558	Japan
Goto	Yasushi	National Cancer Center Hospital	5-1-1, Tsukiji	Chuo-Ku	Tokyo	104-0045	Japan
Hosomi	Yukio	National Cancer Center Hospital Tokyo Metropolitan Cancer & Infectious Disease Center	3-18-22 Honkomagome	Bunkyo-ku	Tokyo	113-8677	Japan

(Continues)

Appendix 1. Continued

Investigator last name	Investigator first name	Institution	Address	City	State/province	Postal code	Country
Sakai	Hiroshi	Saitama Cancer Center	780 Oazakomuro Inamachi	Kita-Adachi	Saitama	362-0806	Japan
Takiguchi	Yuichi	Chiba University Hospital	1-8-1 Inohana Chuo-Ku	Chiba	Chiba	260-8677	Japan
Kim	Young Hak	Kyoto University Hospital	54 Shogoin Kawaharacho Sakyo-Ku	Kyoto	Kyoto	606-8507	Japan
Kurata	Takayasu	Kansai Medical University Hospital	2-3-1 Shinmachi	Hirakata	Osaka	573-1191	Japan
Yamaguchi	Hiroyuki	Nagasaki University Hospital	1-7-1 Sakamoto	Nagasaki		852-8501	Japan
Daga	Haruko	Osaka City General Hospital	2-13-22 Miyakojima-hondori Miyakojima-ku	Osaka	Osaka	534-0021	Japan
Okamoto	Isamu	Kyushu University Hospital	3-1-1 Maidashi Higashi-Ku	Fukuoka	Fukuoka	812-8582	Japan
Satouchi	Miyako	Hyogo Cancer Center	13-70 Kitaoji-Cho	Akashi	Hyogo	673-8558	Japan
Ikeda	Satoshi	Kanagawa Cardiovascular and Respiratory Center	6-16-1 Tomiokahigashi Kanazawa-Ku	Yokohama	Kanagawa	236-0051	Japan
Kasahara	Kazuo	Kanazawa University Hospital	13-1 Takara-Machi	Kanazawa	Ishikawa	920-8641	Japan
Atagi	Shinji	National Hospital Organization Kinki-Chuo Chest Medical Center	1180 Nagasone-cho Kita-ku	Sakai	Osaka	591-8555	Japan
Azuma	Koichi	Kurume University Hospital	67 Asahi-Machi	Kurume	Fukuoka	830-0011	Japan
Kumagai	Toru	Osaka International Cancer Institute	3-1-69 Otemae Chuou-ku	Osaka	Osaka	541-8567	Japan
Aoe	Keisuke	Yamaguchi-Ube Medical Center	685 Higashikiwa	Ube	Yamaguchi	755-0241	Japan
Horio	Yoshitsugu	Aichi Cancer Center Hospital	1-1 Kanokoden Chikusa-Ku	Nagoya	Aichi	464-8681	Japan
Yamamoto	Nobuyuki	Wakayama Medical University Hospital	811-1 Kimiidera	Wakayama	Wakayama	641-8510	Japan
Tanaka	Hiroshi	Niigata Cancer Center Hospital	2-15-3 Kawagishi-cho Chuo-ku	Niigata	Niigata	951-8566	Japan
Watanabe	Satoshi	Niigata University Medical & Dental Hospital	1-754, Asahimachidori, Chuo-ku	Niigata	Niigata	951-8520	Japan
Nogami	Naoyuki	National Hospital Organization Shikoku Cancer Center	160 Kou Minamiumemoto-machi	Matsuyama	Ehime	791-0280	Japan
Ozaki	Tomohiro	Kishiwada City Hospital	1001 Gakuhara-Cho	Kishiwada	Osaka	596-8501	Japan
Koyama	Ryo	Juntendo University Hospital	3-1-3 Hongo	Bunkyo-ku	Tokyo	113-8431	Japan
Hirashima	Tomonori	Osaka Habikino Medical Center	3-7-1 Habikino	Habikino	Osaka	583-8588	Japan
Kaneda	Hiroyasu	Osaka City University Hospital	1-5-7 Asahimachi, Abeno-ku	Osaka	Osaka	545-8586	Japan
Tomii	Keisuke	Kobe City Medical Center General Hospital	2-1-1, Minami-machi, Minatojima, Chuo- ku	Kobe	Hyogo	650-0047	Japan

(Continues)

Appendix 1. Continued

Investigator last name	Investigator first name	Institution	Address	City	State/province	Postal code	Country
Fujita	Yuka	National Hospital Organization Asahikawa Medical Center	7-4048 Hanasaki-cho	Asahikawa	Hokkaido	070-8644	Japan
Seike	Masahiro	Nippon Medical School Hospital	1-1-5, Sendagi	Bunkyo-Ku	Tokyo	113-8603	Japan
Nishimura	Naoki	St. Luke's International Hospital	9-1 Akashi-cho	Chuo-Ku	Tokyo	104-8560	Japan
Kato	Terufumi	Kanagawa Cancer Center	2-3-2 Nakao Asahi-Ku	Yokohama	Kanagawa	241-8515	Japan
Ichiki	Masao	National Hospital Organization Kyushu Medical Center	1-8-1 Jigyohama, Chuo-ku	Fukuoka	Fukuoka	810-8563	Japan
Saka	Hideo	Nagoya Medical Center	4-1-1 Sannomaru, Naka-Ku	Nagoya	Aichi	460-0001	Japan
Hirano	Katsuya	Hyogo Prefectual Amagasaki General Medical Center	Higashinaniwacho 2-17-77	Amagashiki City	Hyogo	660-8550	Japan
Nakahara	Yasuharu	National Hospital Organization Himeji Medical Center	68 Honmachi	Himeji	Hyogo	670-8520	Japan
Sugawara	Shunichi	Sendai Kousei Hospital	4-15 Hirose machi, Aoba-ku	Sendai	Miyagi	980-0873	Japan
Ho	James Chung	Queen Mary Hospital	102 Pok Fu Lam Rd Professional Block	Hong Kong		0	Hong Kong
Au	Kwok-Hung	Queen Elizabeth Hospital	30 Gascoigne Rd 11F, Block R	Kowloon		0	Hong Kong
Park	Keunchil	Samsung Medical Center	81 Irwon-Ro, Gangnam-Gu	Seoul	Korea	06351	Korea, South
Kim	Sang-We	Asan Medical Center	88, Olympic-ro 43-Gil	Songpa-gu	Seoul	05505	Korea, South
Min	Young Joo	Ulsan University Hospital	877, Bangeojinsunhwan-doro, Dong-gu	Ulsan	Korea	44033	Korea, South
Lee	Hyun Woo	Ajou University Hospital	206, World cup-ro, Yeongtong-gu	Suwon	Gyeonggi-do	16499	Korea, South
Kang	Jin-Hyoung	Seoul St. Mary's Hospital	222 Banpodaero, Seocho-gu	Seoul	Seoul	06591	Korea, South
An	Ho Jung	Saint Vincent Hospital	93 Jungbu-daero Paldal-Gu o	Suwon	Gyeonggi-do	16247	Korea, South
Lee	Ki Hyeong	Chungbuk National University Hospital	776 Soonhwan-ro1, Seowon-gu	Cheongju-si	Chungcheongbuk-do	28644	Korea, South
Kim	Jin-Soo	Seoul Municipal Boramae Hospital	20, Boramae-ro 5-gil, Dongjak-gu	Seoul		07061	Korea, South
Lee	Gyeong-Won	Gyeong-Sang National University Hospital	79 Gangnan ro	Jin-ju-si	Gyeongsangnam-do	52727	Korea, South
Lee	Sung Yong	Korea University Guro Hospital	148, Gurodongro, Gurogu	Seoul	Korea	08308	Korea, South
Lin	Meng-Chih	Chang Gung Memorial Hospital - Kaohsiung	No. 123 Dapi Rd, Niaosong District	Kaohsiung City		83301	Taiwan
Su	Wu-Chou	National Cheng Kung University Hospital	No. 138 Sheng-Li Rd	Tainan		704	Taiwan

(Continues)

Appendix 1. Continued

Investigator last name	Investigator first name	Institution	Address	City	State/province	Postal code	Country
Hsia	Te-Chun	China Medical University Hospital	No. 2, Yude Rd North District	Taichung City		40447	Taiwan
Chang	Gee-Chen	Taichung Veterans General Hospital	No 160 Chung Kuan Rd, Section 3	Taichung		40705	Taiwan
Wei	Yu-Feng	E-DA Hospital	No. 1, Yida Rd Jiao-Su Village, Yan-Chao District	Kaohsiung		82445	Taiwan
Chiu	Chao-Hua	Taipei Veterans General Hospital	No. 201, Section 2, Shih-Pai Rd Beitou District	Taipei		11217	Taiwan
Shih	Jin-Yuan	National Taiwan University Hospital	No.1, Changde St. Zhongzheng District	Taipei City		10048	Taiwan
Su	Jian	MacKay Memorial Hospital	No. 92, Section 2, Zhongshan North Rd	Taipei City		10449	Taiwan
Non-East Asia							
Chu	Quincy	Cross Cancer Institute	11560 University Ave, Dept of Medical Oncology	Edmonton	AB	T6G 1Z2	Canada
Cortot	Alexis	CHRU de Lille-Hôpital Albert Calmette	Bd du Professeur Jules Leclercq	Lille		59037	France
Pujol	Jean-Louis	Centre Hospitalier Universitaire Lapeyronie	371 Av Du Doyen Gaston Giraud	Montpellier Cedex 5	Montpellier	34295	France
Moro-Sibilot	Denis	CHU Albert Michallon	6 Boulevard De La Chantourne	La Tronche	Grenoble	38049	France
Fabre	Elizabeth	APHP-Hôpital Européen Georges Pompidou	20-40 Rue LeBlanc	Paris		75015	France
Lamour	Corinne	CHU la Miletrie	2 Rue de la Miletrie	Poitiers		86021	France
Bischoff	Helge	Thoraxklinik Heidelberg GmbH	Röntgenstraße 1	Heidelberg	Baden-Württemberg	69126	Germany
Kollmeier	Jens	HELIOS Klinikum Emil von Behring	Walterhöferstraße 11 Lungenklinik Heckeshorn Klinik für Pneumologie	Berlin	Berlin	14165	Germany
Reck	Martin	LungenClinic Grosshansdorf	Wöhrendamm 80	Großhansdorf	Schleswig-Holstein	22927	Germany
Kimmich	Martin	Klinik Schillerhöhe	Solitudestraße 18 Zentrum für Pneumologie & Thoraxchirurgie	Gerlingen	Baden-Württemberg	70839	Germany
Engel-Riedel	Walburga	Kliniken der Stadt Köln GmbH Klinikum Köln-Merheim	Ostmerheimer Straße 200 Lungenklinik	Köln	Nordrhein-Westfalen	51109	Germany
Hammerschmidt	Stefan	Klinikum Chemnitz GmbH	Bürgerstraße 2	Chemnitz	Sachsen	09113	Germany
Schütte	Wolfgang	Städtisches Krankenhaus Martha-Maria Halle-Dölau GmbH	Röntgenstraße 1 Klinik für Innere Medizin II	Halle (Saale)	Sachsen-Anhalt	06120	Germany
Syrigos	Konstantinos	SOTIRIA General Hospital	152 Mesogion Ave	Athens	Greece	11527	Greece

(Continues)

Appendix 1. Continued

Investigator last name	Investigator first name	Institution	Address	City	State/province	Postal code	Country
Novello	Silvia	Azienda Ospedaliero - Universitaria S. Luigi Gonzaga - Orbassano TO	Regione Gonzole, 10	Orbassano	Torino	10043	Italy
Ardizzoni	Andrea	Policlinico S. Orsola Malpighi – Universita di Bologna	Via Albertoni, 15	Bologna		40138	Italy
Pasello	Giulia	IRCCS Istituto Oncologico Veneto	Via Gattamelata, 64	Padova		35128	Italy
Gregorc	Vanessa	IRCCS Ospedale San Raffaele	Via Olgettina, 60	Milano	Milano	20132	Italy
Del Conte	Alessandro	Azienda per l'Assistenza Sanitaria n°5 "Friuli Occidentale"	Via Montereale, 24	Pordenone	PD	33170	Italy
Galetta	Domenico	IRCCS Ospedale Oncologico di Bari	Viale Orazio Flacco, 65	Bari	Bari	70124	Italy
Alexandru	Aurelia	Institutul Oncologic Dr Trestioreanu Bucuresti	Soseaua Fundeni NR. 252	Bucuresti	Sector 2	022328	Romania
Udrea	Anghel Adrian	SC MedisProf SRL	Piata 1 Mai Nr 3	Cluj-Napoca	Cluj	400058	Romania
Juan-Vidal	Óscar	Hospital Universitario La Fe de Valencia	Servicio de Farmacia - Ensayos Clínicos Torre D. Sotano 1 Avda de Fernando Abril Martorell 106	Valencia	Valencia	46026	Spain
Nadal-Alforja	Ernest	Institut Catala d'Oncologia	Gran Via 199-203	L'Hospitalet de Llobregat	Barcelona	08907	Spain
Gil-Bazo	Ignacio	Clinica Universitaria De Navarra	Avd. Pio XII, 36 Servicio de Oncología 8ª planta	Pamplona	Navarra	31008	Spain
Ponce-Aix	Santiago	Hospital Universitario 12 de Octubre	Carretera De Andalucia, Km - 5.4 Serv. de Oncologia Edif. Materno Infantil - 2ª planta	Madrid	Madrid	28041	Spain
Paz-Ares	Luis						
Rubio-Viqueira	Belén	Hospital Universitario Quiron Madrid	C/Diego de Velazquez, 1 Servicio de Oncología Médica planta-1	Pozuelo de Alarcon	Madrid	28223	Spain
Alonso Garcia	Miriam	Hospital Universitario Virgen del Rocio	Avenida Manuel Siurot s/n	Sevilla		41013	Spain
Felip Font	Enriqueta	Hospital Universitari Vall d'Hebron	Passeig Vall d'Hebron, 119-129 Servicio de Oncología	Barcelona	Barcelona	08035	Spain
Fuentes Pradera	Jose	Hospital Universitario Nuestra Señora de Valme	Autovia Sevilla-Cadiz, s/n ONCOLOGY	Sevilla	Sevilla	46014	Spain
Coves Sarto	Juan	Hospital Fundacion Son Llatzer	Ctra Manacor km 4 Servicio de Oncología	Palma de Mallorca	Baleares	07198	Spain
Cicin	Irfan	Trakya University Faculty of Medicine	Balkan Yerleskesi	Edirne		22770	Turkey

(Continues)

Appendix 1. Continued

Investigator last name	Investigator first name	Institution	Address	City	State/province	Postal code	Country
Goksel	Tuncay	Ege University Faculty of Medicine	Kazimdirik Mah. Bornova	Izmir		35100	Turkey
Harputluoglu	Hakan	Inonu University Medical Faculty	Inonu University,Turgut Ozal Medical Center, Elazig Yolu 15.km	Malatya	Turkey	44280	Turkey
Ozyilkan	Ozgur	Baskent Adana Educational Hospital	Karabekir Mah. Gülhatmi Cad. No:37/A 01120, Yuregir	Adana		1250	Turkey
Henning	Ivo	Nottingham City Hospital	Hucknall Road Dept. of Medical Oncology	Nottingham	Nottinghamshire	NG5 1PB	United Kingdom
Popat	Sanjay	Royal Marsden NHS Trust	Fulham Rd	London	Greater London	SW3 6JJ	United Kingdom
Hatcher	Olivia	Charing Cross Hospital	Fulham Palace Rd Department of Oncology	Chelsea	London	W6 8RF	United Kingdom
Mileham	Kathryn	Levine Cancer Institute - Carolinas Medical Center	1021 Morehead Medical Dr Ste 3200	Charlotte	NC	28204	United States
Acoba	Jared	The Queen's Medical Center	701 Ilalo St Ste 323	Honolulu	HI	96813	United States
Garon	Edward	UCLA Medical Center	2020 Santa Monica Blvd	Santa Monica	CA	90404	United States
Jung	Gabriel	Queens Medical Associates	176-60 Union Turnpike Ste 360	Fresh Meadows	NY	11366	United States
Raj	Moses	Allegheny General Hospital	320 East North Ave	Pittsburgh	PA	15212	United States
Martin	William	Pharmatech Oncology Inc	800 Grant St	Denver	CO	80203	United States
Dakhil	Shaker	TRIO – Translational Research in Oncology - US, Inc	10945 Le Conte Ave Ste 3360	Los Angeles	CA	90095	United States

Six sites screened but did not randomize patients.