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RELAY, ramucirumab plus erlotinib versus placebo plus erlotinib in patients with untreated, EGFR-mutated, metastatic non-small cell lung cancer: Europe/United States subset analysis

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ABSTRACT

Background: In *EGFR* mutation-positive NSCLC, dual EGFR/VEGFR inhibition compared to EGFR alone increases anti-tumor efficacy. The Phase III RELAY trial demonstrated superior PFS for ramucirumab plus erlotinib (RAM + ERL) over placebo plus erlotinib (PBO + ERL) (HR 0.591 [95% CI 0.461–0.760], $p<0.0001$). *EGFR* mutated NSCLC is less prevalent in Western versus Asian patients. This prespecified analysis evaluates efficacy and safety of RAM + ERL in EU and US patients enrolled in RELAY.

Patients and Methods: Patients were randomized 1:1 to ERL + RAM (10 mg/kg IV) or PBO Q2W. Treatment continued until unacceptable toxicity or progressive disease. Patients were stratified by geographic region (East Asia vs "other" [EU/US and Canada (EU/US)]). Objectives included PFS, ORR, DoR, OS, PFS2, safety and biomarker analysis.

Results: EU/US subset included 113/449 (25.9%) patients (58 RAM + ERL, 55 PBO + ERL). RAM + ERL improved PFS (20.6 vs 10.9 months, HR 0.605 [95% CI: 0.362–1.010]). ORR and DCR were similar, but median DoR was longer with RAM + ERL (18.0 vs 10.1 months, HR 0.527 [95% CI: 0.296–0.939]). OS and PFS2 were immature at data cut-off (censoring rates 81.0–81.8% and 67.3–79.3%, respectively). Most commonly reported Grade ≥3 TEAE for RAM + ERL was hypertension (17 [29.8%]) and for PBO + ERL, dermatitis acneiform (5 [9.1%]).

Conclusion: EU/US subset analysis showed improved efficacy outcomes for RAM + ERL and a safety profile consistent with the overall population. Ramucirumab is a safe and effective addition to standard-of-care EGFR-TKI for *EGFR* mutation-positive metastatic NSCLC.

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Introduction

Asian and Western patients with lung cancer have different epidemiological characteristics (e.g. risk factors, demographics, and genetic susceptibility), response to targeted therapies and prognosis[1,2], and tumor biomarkers (e.g. epidermal growth factor *[EGFR]* and kirsten rat sarcoma viral oncogene homolog [*KRAS*] mutation).

EGFR mutations occur in 10–20% of Caucasian and 40–60% of Asian patients with non-small cell lung cancer (NSCLC) [3]. While there is considerable data on *EGFR* mutation frequency amongst Asians and Caucasians and the mechanism responsible for the lower frequency of *EGFR* mutations in Western patients is not yet well understood [4,5], the difference may be related to interethnic genetic variation [6].

The majority of the *EGFR* activating mutations identified that confer sensitivity to tyrosine kinase inhibitors (TKIs) occur in exon 19 (Ex19del) or exon 21 (L858R) of the tyrosine kinase domain of EGFR [3, 7-10]. Ex19del is more prevalent among Western patients [11], while L858R is more common among Asian patients [12]. The exact mechanism(s) behind this difference is unclear.

In large Phase III trials, EGFR-TKIs of all generations demonstrated improved progression-free survival (PFS) and response rates in patients harboring Ex19del and L858R *EGFR* mutations, irrespective of region (Europe, Japan, China) or ethnicity [2,13-15].

According to several large epidemiologic studies, East Asian ethnicity predicts a favorable overall survival (OS) in patients with *EGFR* mutation-positive NSCLC compared to non-East-Asians [2,14-17]; therefore, Asian patients may represent a unique subpopulation within *EGFR* mutation-positive NSCLC [18]. Most studies of the first-line EGFR-TKIs landmark trials have been conducted in full Asian populations or with predominant Asian enrollment [3,9,19,20]. Although EGFR-TKIs have demonstrated efficacy as a single agent[12] and in combination with anti-angiogenic therapy[21,22], in trials in Western NSCLC patients with activating *EGFR* mutations there remains a paucity of data.

Ramucirumab (RAM) is a human IgG1 monoclonal antibody vascular endothelial growth factor (VEGF) receptor 2 antagonist. In preclinical EGFR-mutant NSCLC studies, up-regulated EGFR signaling increased VEGF via hypoxia-independent mechanisms, which contributed to EGFR-TKI resistance. Thus, dual blockade of both EGFR and VEGF pathways would be more effective than either approach alone and may show activity in tumors with acquired resistance to EGFR inhibitors [23]. In different clinical trials (NEJ026, CTONG1509, RELAY), dual EGFR/VEGF pathway inhibition considerably improved clinical outcomes [23]. RELAY (NCT02411448), a global phase 3 study, demonstrated superior PFS for RAM + erlotinib (ERL) compared to placebo (PBO) + ERL in patients with previously untreated *EGFR* mutation-positive metastatic NSCLC (median PFS: 19.4 vs 12.4 months; hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.46–0.76; $p<0.0001$) [24]. The safety profile observed in RELAY was consistent with the safety profile of RAM established in previous pivotal studies as well as the known safety profile of ERL and/or events expected to occur within the disease setting of advanced NSCLC [25,26]. The aim of this prespecified subset analysis of the RELAY study was to further evaluate patients enrolled in the EU and US to determine their specific efficacy and safety outcomes.

Patients and methods

Study design

RELAY was a global double-blind, placebo-controlled Phase III study of RAM + ERL versus PBO + ERL in patients with previously untreated *EGFR* mutation-positive metastatic NSCLC. Eligible patients had stage IV metastatic NSCLC with an *EGFR* Ex19del deletion or L858R substitution mutation; no prior treatment with EGFR-TKI or chemotherapy; Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1; no known *EGFR* threonine 790 methionine (T790M) mutation; and no central nervous system (CNS) metastasis. Full eligibility criteria have been previously reported [24]. Randomization was stratified according to geographical region (East Asia vs "other"), gender, *EGFR* mutation type (Ex19del vs Ex21.L858R) and local *EGFR* testing method (therascreen/cobas vs other PCR/sequencing-based methods). Patients, investigators, and all clinical study personnel were masked to the assigned treatment and will continue to be masked until the final analysis of OS. The protocol and amendments were approved by the ethics committees of all participating centers and all patients provided written informed consent before study entry. The trial was conducted according to the Declaration of Helsinki, the International Conference on Harmonization guidelines for good clinical practice, and applicable local regulations [24].

Procedures

Patients were randomized 1:1 to receive 150 mg daily oral ERL plus 10 mg/kg intravenous RAM or PBO every 2 weeks. Dose adjustments were previously described [24]. Treatment continued until disease progression or unacceptable toxicity.

Tumor assessments (computed tomography or magnetic resonance imaging scans) were conducted within 28 days before randomization, every 6 weeks from the start of study therapy to 72 weeks, then every 12 weeks until disease progression or study discontinuation, and at the 30-day short-term follow-up visit. Patients who discontinued study treatment were followed up for survival until study completion; at the time of this analysis, follow-up for overall survival is still ongoing. Post-discontinuation treatment was at the discretion of the investigator [24].

Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Liquid biopsy samples at baseline and the 30-day follow-up visit were assessed for *EGFR* T790M mutation status using Guardant360 next-generation sequencing (Guardant Health; Redwood City, CA, US).

Enrollment by region

Randomized patients stratified by geographic region "other" comprised patients from the EU, US and Canada (EU/US). This EU/US subset consisted of 113 patients (25.2% of the overall population) enrolled from 9 countries: Canada, France, Germany, Italy, Romania, Spain, Turkey, United Kingdom, and the United States. Enrollment occurred between January 2016 and February 2018.

Outcomes

The primary objective was PFS (investigator assessed) [22]. A blinded, independent review of PFS was also conducted. Secondary objectives included overall response rate (ORR; complete response [CR] + partial response [PR]), disease control rate (DCR; CR + PR + stable disease), duration of response (DoR), OS, and safety and toxicity profiles. Prespecified exploratory endpoints included PFS2, time to CNS metastasis (defined as time from randomization to CNS metastases), and biomarker analyses. PFS2 is the time from randomization to second objective disease progression, or death from any cause, whichever comes first.

Statistical considerations

Full statistical methodology has been reported previously [24]. Efficacy endpoints were assessed in the EU/US intent-to-treat population, which included all randomly assigned patients from EU/US study sites. Safety endpoints were assessed in the EU/US safety population, including all patients who received at least 1 dose of study treatment. PFS, OS, DoR, and PFS2 were estimated using the Kaplan-Meier method [27] and Cox proportional hazards models [28]. Prespecified subgroup

analyses were conducted using an unstratified Cox model. ORR and DCR were calculated as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). ORR observed in each treatment group was compared using the Cochran-Mantel-Haenszel test. DoR was analyzed for responders only. Clinical and laboratory toxic effects were graded using National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.0. *EGFR* T790M mutation frequency analyses were done in patients who had disease progression by data cut-off and had available central next-generation circulating tumor DNA (ctDNA) sequencing results.

Results

Baseline characteristics

The EU/US subset (113 patients [RAM + ERL, $n = 58$ and PBO + ERL, $n = 55$]) were mostly Caucasian (90% in RAM + ERL, 87% in PBO + ERL). Baseline patient and clinical characteristics of the EU/US population were balanced between treatment arms and reflective of an *EGFR* mutated overall patient population (Table 1).

In comparison to the overall population, the proportion of never smokers was lower (52% vs 61%). The proportion of patients with an *EGFR* Ex19del deletion was higher among the EU/US subset as compared to the overall population (66% vs 54%). Additionally, a higher proportion of patients in the EU/US subset were locally tested for their *EGFR* mutation with a regulatory approved test (therascreen/cobas) compared to the overall population (61% vs 44%) (Table 1). Other baseline characteristics in the EU/US subset were consistent with that of the overall population.

Patient disposition

At the time of the primary data cut-off (23 January 2019), 22 (38%) of patients in the RAM + ERL arm and 17 (31%) of patients in the PBO + ERL arm remained on study treatment (Supplemental Table 1). The main reason for study treatment discontinuation was progressive disease (41% and 58% for RAM + ERL and PBO + ERL, respectively). The median duration of patient follow-up was 17.6 months (0.5–33.1 months).

Progression-free survival

RAM + ERL demonstrated longer PFS compared to PBO + ERL (median PFS: 20.6 months [95% CI: 14.7–26.0] vs 10.9 months [95% CI: 8.4–19.4], HR 0.605 [95% CI: 0.362–1.010]) (Fig. 1). A sensitivity analysis of PFS for RAM + ERL versus PBO + ERL according to blinded independent radiological review showed PFS results consistent with the primary investigator-assessed PFS analysis (unstratified HR 0.654 [95% CI: 0.383–1.117]). Similar results to the investigator-assessed PFS were also observed in the prespecified Caucasian race subgroup, which excludes patients of non-Caucasian race enrolled in EU/US region ($n = 100$; unstratified HR 0.618 [95% CI: 0.357–1.070]).

In addition, PFS by *EGFR* mutation type (Ex19del or Ex21.L858R) in the EU/US subset was analyzed (Supplemental Figure 1). In patients with Ex19del, the median PFS was 20.6 months (95% CI: 12.5–28.1) versus 13.5 months (95% CI: 8.4–27.6) in the RAM + ERL versus PBO + ERL arm, respectively (unstratified HR 0.652 [95% CI: 0.335–1.267]); whereas, in patients with Ex21.L858R, median PFS was 15.2 months (95% CI: 10.7–26.0) versus 9.6 months (95% CI: 3.1–11.0), respectively (unstratified HR 0.468 [95% CI: 0.202–1.085]).

Other prespecified subgroup analyses for PFS, by gender, age, ECOG PS, smoking history, disease stage, and *EGFR* testing method, favored the RAM + ERL treatment arm (Supplemental Figure 2). An apparent interaction between treatment effect and local EGFR testing method was observed, which showed a larger PFS benefit for patients tested by the therascreen®/cobas® assay compared to an 'other' test. However, results from central tumor testing indicated the difference was not due to false positives from local assay variability. Analyses of other factors did not identify a cause for the PFS results by testing method subgroup. Regardless of the local EGFR testing method used, evidence of a PFS treatment benefit was observed in patients.

Tumor response

ORR for RAM + ERL compared to PBO + ERL was 74.1% versus 76.4%; DCR was 98.3% and 94.5%, respectively. Individual patient level data for the best percent change from baseline in target lesions is shown in Supplemental Figure 3. In both treatment arms, the majority of patients (>70%) had a PR; 2 patients in the PBO + ERL arm and no patients in the RAM + ERL had progressive disease as best tumor response. RAM + ERL improved DoR compared to PBO + ERL (Fig. 2). The median DoR for RAM + ERL in the EU/US subset was 18.0 months (95% CI: 12.7–22.0) compared to 10.1 months (95% CI: 7.1–17.7) for PBO + ERL (unstratified HR 0.527 [95% CI: 0.296–0.939]).

Interim overall survival

As of data cut-off, the interim OS results were immature with a

Table 1
EU/US Subset and Overall RELAY Baseline Characteristics.

Baseline Characteristic, n (%)		EU/US Subset $N = 113$		Overall Study Population $N = 449$	
		RAM + ERL n = 58	PBO + ERL n = 55	RAM + ERL n = 224	PBO + ERL n = 225
Sex	Female	34 (59)	33 (60)	141 (63)	142 (63)
Age	Median (min-max), years	65 (27–83)	65 (23–89)	65 (27–86)	64 (23–89)
Race	Caucasian	52 (90)	48 (87)	52 (23)	48 (21)
	Asian	6 (10)	4 (7)	172 (77)	174 (77)
	American Indian or Alaska Native	0	1 (2)	0	1 (<1)
	Black or African American	0	1 (2)	0	1 (<1)
	Missing	0	1 (2)	0	1 (<1)
Smoking history	Never	29 (50)	30 (55)	134 (60)	139 (62)
ECOG PS	0	30 (52)	28 (51)	116 (52)	119 (53)
Disease classification	Primary metastatic	49 (85)	45 (82)	195 (87)	191 (85)
	Recurrent metastatic	9 (16)	10 (18)	29 (13)	34 (15)
EGFR mutation type[a]	Exon 19 deletion	39 (67)	36 (66)	123 (55)	120 (53)
	Exon 21 (L858R) mutation	19 (33)	19 (35)	99 (44)	105 (47)
EGFR testing method[a]	Therascreen® or Cobas®	34 (59)	34 (62)	96 (43)	101 (45)
	Other[b]	24 (41)	21 (38)	127 (57)	124 (55)

[a]Determined by local testing; [b]PCR and sequencing-based methods.
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; ERL = erlotinib; EU/US = EU, US and Canada; max = maximum; min = minimum; *n* = number of patients per category; *N* = number of patients in population; PBO = placebo; PCR = polymerase chain reaction; RAM = ramucirumab.

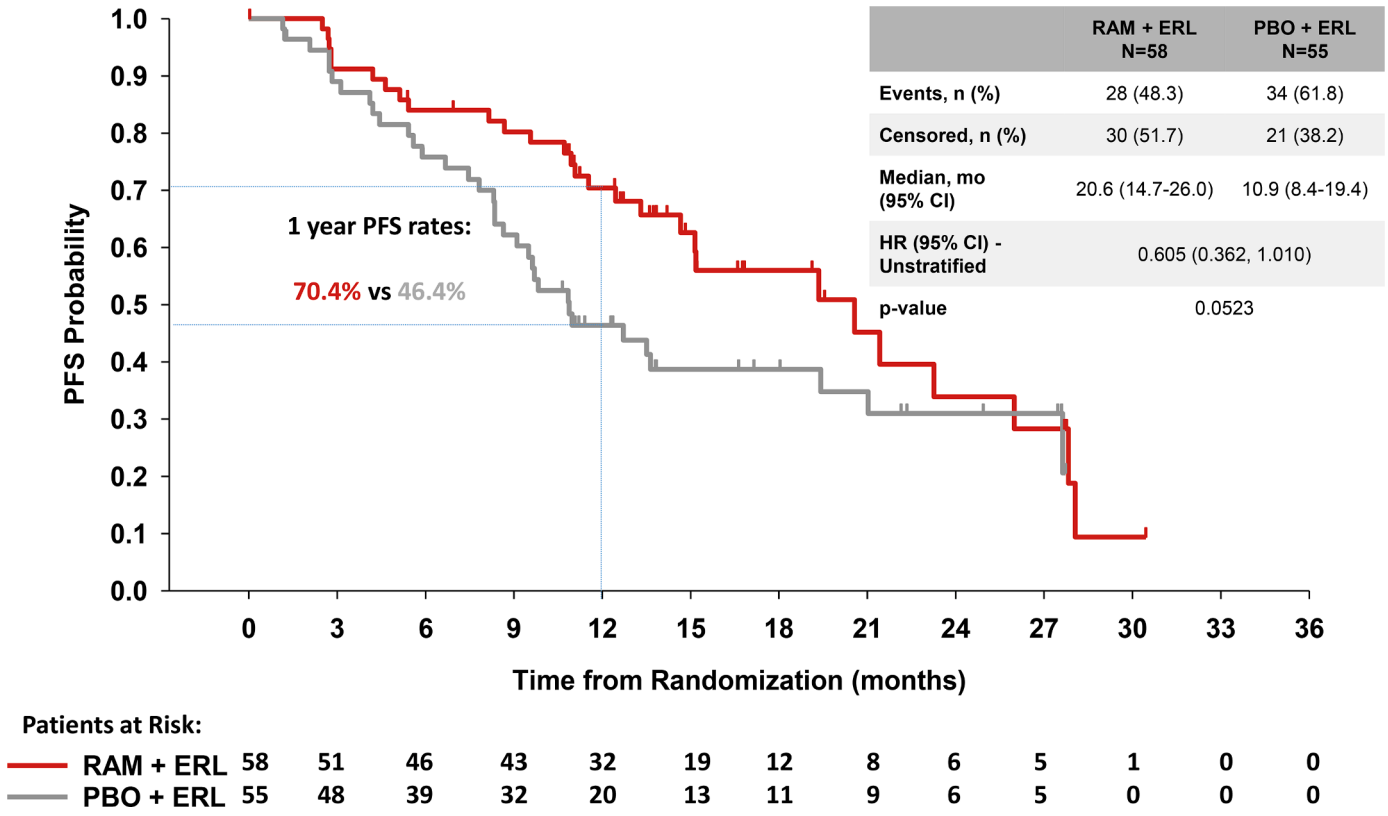

Fig. 1.. RELAY Primary Endpoint: Progression Free Survival (Investigator-Assessed) in the EU/US Subset. Abbreviations: CI = confidence interval; ERL = erlotinib; HR = hazard ratio; mo = months; *n* = number of patients per category; *N* = number of patients in population; PFS = progression-free survival; PBO = placebo; RAM = ramucirumab.

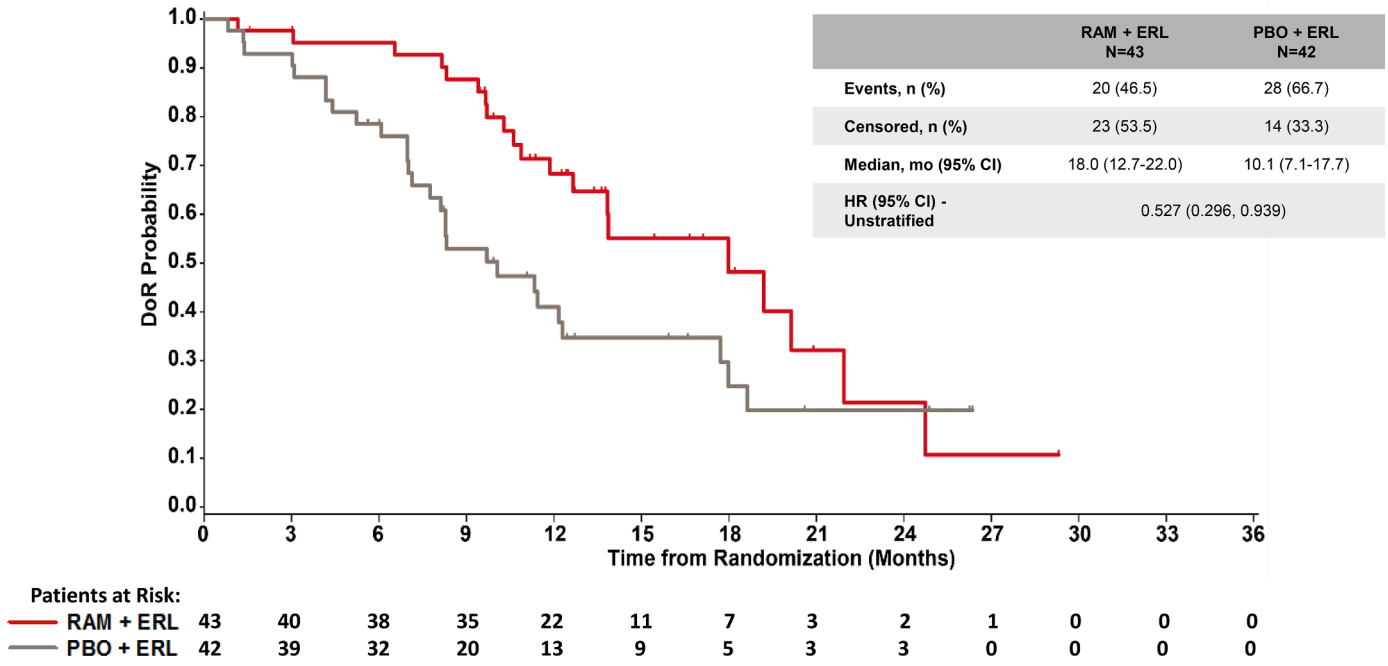

Fig. 2. RELAY Duration of Tumor Response in the EU/US Subset. Abbreviations: CI = confidence interval; DoR = duration of response; ERL = erlotinib; HR = hazard ratio; mo = months; *n* = number of patients per category; *N* = number of patients in population; PBO = placebo; RAM = ramucirumab.

censoring rate of 82% (unstratified HR 1.096 [95% CI: 0.465–2.582]). The EU/US subset had a total of 21 death events (out of a total of 79 observed in the overall population), with 11 on RAM + ERL and 10 on PBO + ERL. Final analysis will be conducted when at least 300 OS events have occurred.

Progression-free survival 2

PFS2 results were immature (censoring rate 73.5%), with only 30 PFS2 events (12 on RAM + ERL and 18 on PBO + ERL). Median PFS2 was not reached in either arm; a trend towards improvement in PFS2 was seen for RAM + ERL versus PBO + ERL (HR 0.632 [95% CI: 0.304–1.313]) (Fig. 3).

Time to diagnosis of CNS metastases

No patients in the EU/US subset developed brain metastases as site of disease progression. A total of 10 patients (RAM + ERL, $n = 2$; PBO + ERL, $n = 8$) reported brain as site of progression, but they were all of East Asian origin. Of note, the small sample size reduces the rigor of this analysis, and the outcome should be taken with some reservation.

Treatment exposure

In the RAM + ERL arm, median (minimum–maximum) duration of exposure (censored analysis excluding 22 [38.6%] patients still on treatment) to RAM was 13.8 (10.1–15.2) months and to ERL was 14.8 (12.7–20.7) months. In the PBO + ERL arm, the duration of exposure (censored analysis excluding 17 [30.9%] patients still on treatment) to PBO was 9.8 (7.4–13.5) months and to ERL was 9.8 (7.9–13.8) months.

Dose adjustments of RAM occurred in 44 (77.2%) patients, while dose adjustments of PBO occurred in 36 (65.5%) patients. The percentage of patients that required dose adjustments of ERL was similar between treatment arms (37 [64.9%] for RAM + ERL and 37 [67.3%] for PBO + ERL). The most common reason for dose reductions, dose delays, and dose omissions were treatment-emergent adverse events (TEAEs). Dose reduction of RAM was observed for 2 patients total, due to proteinuria; other TEAEs leading to dose reduction of PBO were reported in single patients only. The most common TEAE resulting in RAM or PBO dose delays was blood bilirubin increased (8 [14.0%] on RAM + ERL vs 4 [7.3%] on PBO + ERL). Dose omissions due to blood bilirubin increased (2 [3.5%] on RAM + ERL vs 4 [7.3%] on PBO + ERL) and proteinuria (3 [5.3%]) on RAM + ERL vs 0 on PBO + ERL) were the most frequently reported. In both treatment arms, the most common TEAEs leading to ERL dose reductions and omissions were dermatitis acneiform (reductions: 4 [7.0%] on RAM + ERL vs 4 [7.3%] on PBO + ERL) and diarrhea (omissions: 7 [12.3%] on RAM + ERL vs 6 [10.9%] on PBO + ERL).

Treatment-emergent adverse events

The safety overview is shown in Table 2. All patients had at least 1 TEAE (Table 3); 43 (75%) patients in the RAM + ERL arm and 37 (67%) patients in the PBO + ERL arm had a Grade ≥ 3 TEAE. The most common

Table 2
EU/US Subset Safety Overview.

Events, n (%)	EU/US Subset RAM + ERL N = 57	PBO + ERL N = 55
Any TEAE	57 (100.0)	55 (100.0)
Grade ≥3 TEAEs	43 (75.4)	37 (67.3)
Any SAE	14 (24.6)	8 (14.5)
Discontinued all study treatment due to AEs	6 (10.5)	2 (3.6)
Discontinued due to SAE	1 (1.8)	1 (1.8)
AEs leading to death, on study treatment[a]	1 (1.8)	0

[a] Related to study treatment (hemothorax) as assessed by the investigator.
Abbreviations: ERL = erlotinib; EU/US = EU, US and Canada; N = number of patients in population; PBO = placebo; RAM = ramucirumab; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

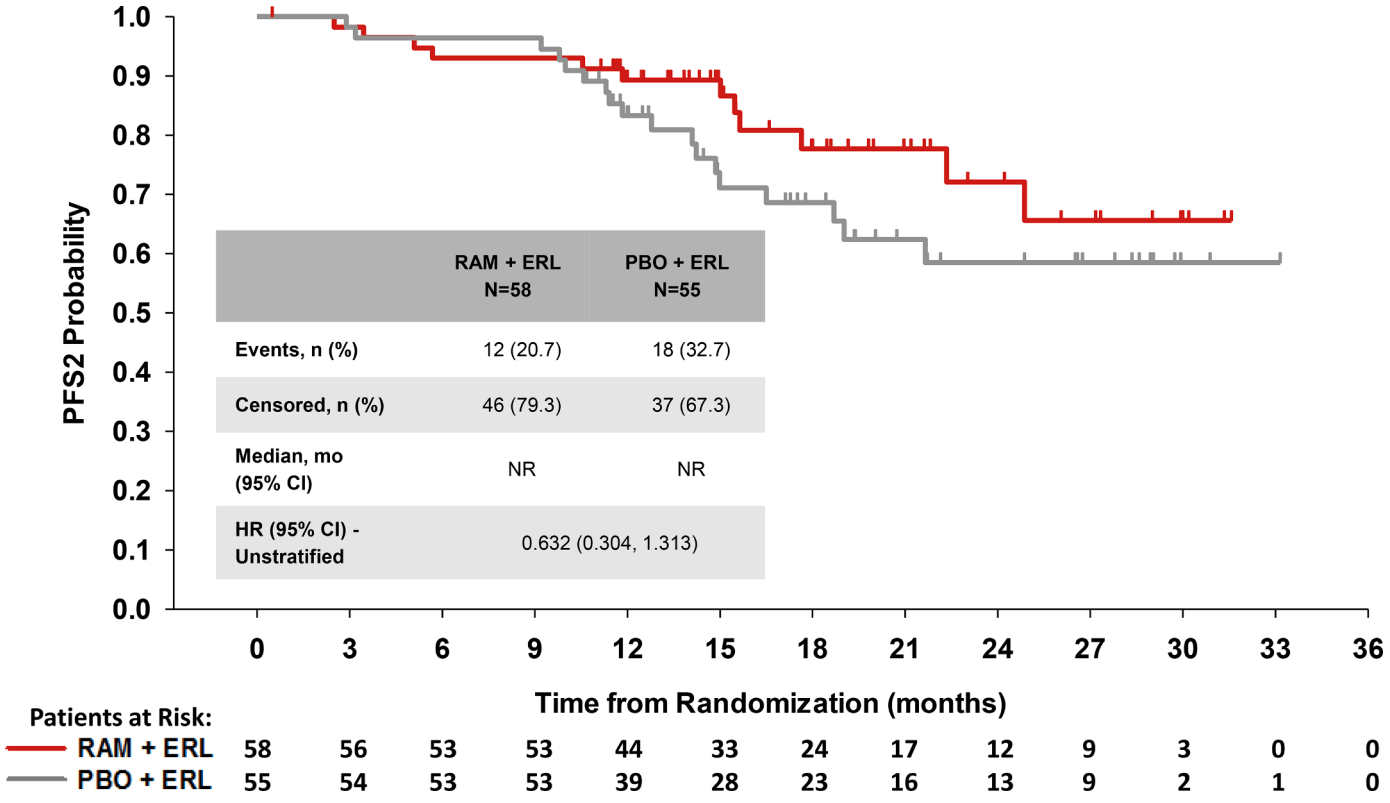

Fig. 3. RELAY Progression-Free Survival 2 in the EU/US Subset. Abbreviations: CI = confidence interval; ERL = erlotinib; HR = hazard ratio; mo = months; n = number of patients per category; N = number of patients in population; NR = not reached; PBO = placebo; PFS2 = the time from randomization to 2nd objective disease progression, or death from any cause, whichever comes first; RAM = ramucirumab.

Table 3
Treatment-Emergent Adverse Events Occurring in ≥20% of the Safety Population, in the EU/US Subset.

	EU/US Subset			
	RAM + ERL N = 57		PBO + ERL N = 55	
Preferred Term, n (%)[a]	Any Grade	Grade ≥3	Any Grade	Grade ≥3
At least one TEAE	57 (100.0)	43 (75.4)	55 (100.0)	37 (67.3)
Diarrhea	43 (75.4)	7 (12.3)	42 (76.4)	1 (1.8)
Acneiform dermatitis	20 (35.1)	3 (5.3)	21 (38.2)	5 (9.1)
Paronychia	18 (31.6)	1 (1.8)	14 (25.5)	1 (1.8)
Hypertension	30 (52.6)	17 (29.8)	7 (12.7)	4 (7.3)
Increased ALT	18 (31.6)	4 (7.0)	10 (18.2)	1 (1.8)
Increased AST	19 (33.3)	4 (7.0)	7 (12.7)	2 (3.6)
Stomatitis	17 (29.8)	2 (3.5)	20 (36.4)	1 (1.8)
Dry skin	22 (38.6)	0	25 (45.5)	2 (3.6)
Proteinuria	13 (22.8)	2 (3.5)	6 (10.9)	0
Alopecia	17 (29.8)	0	19 (34.5)	0
Epistaxis	16 (28.1)	0	5 (9.1)	0
Increased blood bilirubin	13 (22.8)	1 (1.8)	10 (18.2)	2 (3.6)
Decreased appetite	15 (26.3)	1 (1.8)	15 (27.3)	0
Nausea	14 (24.6)	2 (3.5)	14 (25.5)	0
Pruritis	19 (33.3)	1 (1.8)	21 (38.2)	2 (3.6)
Edema peripheral	13 (22.8)	0	2 (3.6)	0
Cough	23 (40.4)	0	14 (25.5)	0
Pyrexia	11 (19.3)	0	3 (5.5)	0
Constipation	11 (19.3)	0	11 (20.0)	0
Rash	22 (38.6)	0	26 (47.3)	3 (5.5)
Fatigue	18 (31.6)	3 (5.3)	13 (23.6)	0

[a] Includes a single Grade 5 toxicity of hemothorax.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ERL = erlotinib; *n* = number of patients per category; EU/US = EU, US and Canada; *N* = number of patients in population; PBO = placebo; RAM = ramucirumab; TEAE = treatment-emergent adverse event.

Grade ≥ 3 TEAEs were hypertension (17 [30%]) and diarrhea (7 [12%]) in the RAM + ERL arm and dermatitis acneiform (5 [9%]) and hypertension (4 [7%]) in the PBO + ERL arm. The events were consistent with the known safety profiles of RAM and ERL.

The percentage of patients who discontinued all study treatment due to an AE or serious AE (SAE) was 11% in the RAM + ERL arm and 4% in the PBO + ERL arm. One patient in the RAM + ERL died due to hemothorax, which was considered by the investigator to be related to study treatment (Table 2).

Adverse events of special interest

Adverse events of special interest (AESIs) were prespecified based on known AEs associated with other anti-angiogenic agents in the same pharmacological class as RAM or that were observed preclinically or in previous clinical studies (Supplemental Table 2). Of the AESIs occurring in at least 10% of the patients (any grade and regardless of treatment group), most were Grade 1 and 2, with the exception of hypertension. Grade 3 or higher AESIs occurring in ≥5% of patients included hypertension (30% vs 7%; only Grade 3) and liver failure/liver injury (16% vs 7%) in RAM + ERL versus PBO + ERL, respectively. Alanine aminotransferase increased was the only Grade ≥3 laboratory value within the AESIs observed in ≥5% of patients (7% on RAM + ERL vs 2% on PBO + ERL).

Post-discontinuation therapy

Of all patients in the US/EU population, 26 of 58 (44.8%) patients in RAM + ERL and 34 of 55 (61.8%) patients in PBO + ERL continued to first subsequent line of therapy (FST); respectively, 22 (37.9%) and 17 (30.9%) patients were still on treatment at the time of data cut-off (Supplemental Table 3). EGFR-TKIs were the most frequently used FST regardless of treatment arm (16 [61.5%] patients in RAM + ERL vs 24 [70.6%] patients in PBO + ERL), with osimertinib used in 5 (19.2%) and 13 (38.2%) of patients, respectively.

Chemotherapy was utilized as FST in 8 (30.8%) patients on RAM + ERL and 9 (26.5%) on PBO + ERL. At the time of database lock, too few patients had continued to second-subsequent line of therapy preventing any meaningful interpretation (7 and 8 patients on RAM + ERL and PBO + ERL, respectively; Supplemental Table 3).

T790M rates

In line with the eligibility criteria, no patients in the EU/US subset had *EGFR* T790M mutations detected centrally at baseline. Post-progression results were available for 24 patients (9 patients on RAM + ERL; 15 on PBO + ERL) whose disease progressed before data cut-off and who had *EGFR*-activating mutation (Ex19del or Ex21.L858R) detected at the 30-day follow-up. In this group, the proportion of patients with a T790M mutation was similar between treatment arms (RAM + ERL, 4/9 patients, 44% [95% CI: 18.9–73.3]; PBO + ERL, 5/15 patients, 33% [95% CI: 15.2–58.3]) (Supplemental Table 4).

Discussion

The global RELAY study showed superior PFS for RAM + ERL versus PBO + ERL in patients with previously untreated metastatic *EGFR* mutated NSCLC (median PFS: 19.4 vs 12.4 months; HR: 0.591 [95% CI: 0.461–0.760], $p<0.0001$) [24]. In RELAY, patients were stratified for variables with potential influence on the primary endpoint, PFS, and as such did include region (East Asia vs 'other'). Although the EU/US ('other') subgroup analysis is not powered to demonstrate significant improvement, RAM + ERL demonstrated a clinically meaningful difference in efficacy over PBO + ERL (median PFS 20.6 vs 10.9 months, HR 0.605 [95% CI: 0.362–1.010]) which was consistent with the overall population. 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 [29]. Patients with Ex19del had a median PFS of 20.6 months versus 13.5 months in the RAM + ERL versus PBO + ERL arm (unstratified HR 0.652 [95% CI: 0.335–1.267]), whereas patients with Ex21.L858R had a median PFS of 15.2 months versus 9.6 months (unstratified HR 0.468 [95% CI: 0.202–1.085]). RAM + ERL also improved DoR (median DoR 18.0 vs 10.1 months, HR 0.527 [95% CI: 0.296–0.939]), to a similar extent as reported in the overall population [24]. ORR and DCR were also consistent with the overall population with no difference detected between treatment arms [24]. Of note, 2 patients in the PBO + ERL arm experienced a best overall response of progressive disease compared to none in the RAM+ERL arm.

Additionally, the EU/US subset safety profile of RAM + ERL was similar with that reported in the overall population and manageable and consistent with the established safety profile of ramucirumab and erlotinib [25,26]. The higher levels of Grade ≥3 toxicities in the RAM + ERL arm did not hinder the duration of study treatment. The longer exposure in the RAM + ERL arm and similar relative dose intensities of study drugs between treatment arms attests to the tolerability of the combination regimen. While the percentage of patients in the RAM + ERL arm that discontinued all study treatment due to an AE was similar for the EU/US and overall population (11% vs 13%, respectively), the percentage of patients who discontinued PBO + ERL was lower in the EU/US subset (4% vs 11%, respectively) [24].

In total, 25% of the overall RELAY population was enrolled in Europe and US. Baseline patient and disease characteristics for the EU/US subset were reflective of an *EGFR* mutated NSCLC population and well-balanced between treatment arms, thereby reducing potential bias due to these factors in assessing efficacy results. The higher Ex19del rate in the EU/US subset as compared to the overall population is aligned with what has been reported [12].

The observations made for the subgroup analysis by region were similar to that by race; a sensitivity analysis excluding patients that were not Caucasian within the EU/US subset demonstrated a consistent PFS

HR (EU/US subset: HR 0.605 [95% CI: 0.362–1.010]; Caucasian race subgroup: HR 0.618 [95% CI: 0.357–1.070]). A similar observation was shown in the ramucirumab REVEL NSCLC study; no treatment difference was detected based on region ("other" vs East Asia) or race [30].

First-line EGFR-TKI studies in NSCLC have shown consistent PFS regardless of race [7,9,10]. Conversely, in the FLAURA trial, osimertinib did show an apparent difference in the magnitude of OS treatment effect between Asian and non-Asian patients (HR 1.00 [95% CI: 0.75–1.32] vs HR 0.54 [95% CI: 0.38–0.77]) [31]. While osimertinib is the preferred treatment option in EGFR untreated *EGFR* mutation-positive metastatic NSCLC, RAM + ERL is a viable treatment option for the subset of patients without CNS metastases[32-33] or for those patients who are not suitable for or have no access to osimertinib.

EGFR T790M is the main mechanism of resistance with treatment of first and second generation EGFR-TKIs [34-36]. In the RELAY EU/US subset, the T790M mutation frequencies at disease progression were similar between the RAM + ERL versus PBO + ERL arm, though sample sizes were small. Like the overall population [24], RAM + ERL does not seem to prevent the emergence of the *EGFR* T790M mutation. For patients that developed a T790M mutation, subsequent administration of a 3rd generation TKI may be a practical therapeutic option to further improve treatment outcomes.

Since most first-line EGFR-TKI trials have occurred in majority Asian populations [3,9,19,20], the ability to generalize the results across populations remains debatable. Currently, there have been a few small studies on EGFR-TKI in combination with anti-angiogenic therapies in predominantly Western populations [21,22]. The RELAY EU/US subset size is comparable to previous smaller studies and not powered for outcome measures, although the consistency with the larger overall RELAY population is strongly supportive of the observed effects [21,22]. The RELAY EU/US subset analysis, which further examined RAM plus EGFR-TKI in a Western population, suggests first-line RAM + ERL is effective and a safe treatment option for Western patients with *EGFR* mutation-positive NSCLC. Therefore, although the majority of RELAY patients were enrolled in East Asia, the validity and generalizability of the study results to a Western population appears to be supported.

Conclusion

Results of the EU/US subset analysis showed improved efficacy outcomes for RAM + ERL and a safety profile consistent with the overall population. The RELAY regimen is a treatment option for initial treatment of *EGFR* mutation-positive metastatic NSCLC. The results of RELAY are considered applicable to all patients per the proposed indication, regardless of patient origin.

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Declaration of Competing Interest

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Supplementary materials

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