



Ramucirumab Plus Erlotinib Versus Placebo Plus Erlotinib in Patients With Untreated Metastatic EGFR-Mutated NSCLC: RELAY Japanese Subset

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ABSTRACT

Introduction: The phase 3 RELAY global study (NCT02411448) revealed significant improvement in progression-free survival (PFS) with ramucirumab plus erlotinib (RAM + ERL) compared with placebo plus ERL (PL + ERL) in untreated *EGFR*-mutated metastatic NSCLC (hazard ratio [HR] = 0.59 [95% confidence interval (CI): 0.46–0.76, $p < 0.0001$]). This prespecified analysis evaluates efficacy, safety, and postprogression *EGFR* T790M rates of RELAY patients enrolled in Japan.

Methods: Patients were randomized (1:1) to oral ERL (150 mg/d) plus intravenous RAM (10 mg/kg) or PL every 2 weeks. End points included PFS (primary), safety (secondary), and biomarker analyses (exploratory). Plasma samples collected at baseline and poststudy treatment discontinuation were evaluated for *EGFR* T790M mutations by next-generation sequencing.

Results: The Japanese subset included 211 of 449 (47.0%) RELAY patients (RAM + ERL, $n = 106$; PL + ERL, $n = 105$). Median PFS was 19.4 versus 11.2 months for RAM + ERL versus PL + ERL treatment (HR = 0.610 [0.431–0.864]) in the Japanese intent-to-treat population, 16.6 versus 12.5 months (HR = 0.701 [0.424–1.159]) in the *EGFR* exon 19 deletion subgroup, and 19.4 versus 10.9 months (HR = 0.514 [0.317–0.835]) in the *EGFR* exon 21 L858R subgroup, respectively. Adverse events of grade 3 or above with RAM + ERL included hypertension (24.8%, all grade 3) and dermatitis acneiform (23.8%). Postprogression treatment-emergent T790M rates were similar between arms (RAM + ERL: 47%, 9 of 19 patients; PL + ERL: 50%, 20 of 40 patients).

Conclusions: Clinically meaningful efficacy was observed with RAM + ERL versus PL + ERL in the RELAY Japanese

subset, with no new safety concerns. Postprogression T790M rates were similar across treatment arms, indicating the addition of RAM did not affect the ERL-associated *EGFR* T790M rates at disease progression.

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Introduction

Activating mutations in the *EGFR* gene are important drivers in NSCLC, making *EGFR*-mutated NSCLC amenable to precision medicine.^{1,2} *EGFR* tyrosine kinase inhibitors (TKIs), the standard first-line treatment for *EGFR*-mutated NSCLC,^{3,4} have different affinities for specific *EGFR* mutations.^{5,6} The clinical benefit with *EGFR* TKIs is greater in patients with exon 19 deletions (ex19dels) versus an exon 21 L858R (ex21.L858R) point mutation.^{7,8} The prevalence of *EGFR* mutations is higher in Asian and Japanese populations (approximately 40%) than in White populations (approximately 20%).⁹ In contrast to White patients, ex21.L858R is more common than ex19del in Japanese patients.¹⁰

Many patients with NSCLC who receive first-line *EGFR* TKIs acquire the *EGFR* T790M resistance mutation.¹¹ Osimertinib is the only targeted treatment against *EGFR* T790M and is approved in Japan for first- and

second-line treatment of patients with *EGFR*-mutated NSCLC.^{3,4} Nevertheless, the mechanisms of resistance to osimertinib are heterogeneous and mostly not targetable with approved small-molecule inhibitors; thus, the only remaining treatment options at the time of progression are chemotherapy-based regimens or immunotherapy.^{3,12,13} Chemotherapy efficacy is limited by its toxicity, and immunotherapy has not been found to be effective in *EGFR*-mutated NSCLC. Therefore, treatment strategies that enhance EGFR TKI efficacy and prolong the chemotherapy-free period are desired.

The EGFR and vascular endothelial growth factor pathways are interconnected, and dual inhibition reduces angiogenesis and abrogates tumor resistance to EGFR TKIs.^{14,15} Targeting both pathways is therefore a viable strategy to improve outcomes in *EGFR*-mutated NSCLC.^{16,17} RELAY was a global, phase 3, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of the addition of ramucirumab (RAM), a human IgG1 vascular endothelial growth factor receptor 2 antagonist, to erlotinib (ERL) in treatment-naïve *EGFR*-mutated metastatic NSCLC.¹⁸ Progression-free survival (PFS) was superior with RAM plus ERL versus placebo plus ERL (median PFS = 19.4 versus 12.4 mo; hazard ratio [HR] = 0.59 [95% confidence interval (CI): 0.46–0.76, $p < 0.0001$]), and the safety profile was consistent with the known safety profiles of RAM and ERL monotherapy.^{18–20} *EGFR* T790M mutation rates after disease progression were similar between treatment arms, indicating subsequent treatment with a T790M-targeting drug remains possible.¹⁸

Treatment selection after progression on EGFR TKI therapy depends on the mechanism of resistance. The challenge of obtaining tumor biopsies during and after treatment can be overcome using plasma samples containing circulating tumor DNA.²¹ Blood samples are less invasive than tissue biopsies, and high concordance between tumor and circulating tumor DNA has been observed using digital polymerase chain reaction and next-generation sequencing (NGS) for T790M analysis and driver mutation detection.^{22,23}

Because the prevalence of *EGFR*-mutated NSCLC in patients from Japan is relatively high and the RELAY Japanese population constituted almost half of the overall RELAY population, we conducted subgroup analyses of clinical efficacy, safety, and postprogression T790M rates in the RELAY Japanese population.

Materials and Methods

Study Design and Participants

RELAY was a global, phase 3, randomized, double-blind, placebo-controlled study in patients with untreated *EGFR*-mutated metastatic NSCLC (www.clinicaltrials.gov: NCT02411448).¹⁸ The RELAY study protocol was

approved by the ethics review board of each site, and the study was conducted in accordance with the Declaration of Helsinki, The Council of International Organizations of Medical Sciences International Ethical Guidelines, Good Clinical Practice guidelines, and local guidelines. All patients provided written informed consent. Eligibility criteria have been previously published and are briefly described in [Supplementary Materials](#).^{18,24}

Randomization and Treatment Protocol

Patients were randomized (1:1) to RAM (10 mg/kg intravenously every 2 wk) plus ERL (150 mg orally once daily) (RAM + ERL) or placebo (PL) plus ERL (PL + ERL). Study drugs were assigned using the Interactive Web Response System. Masking of patients, investigators, and all clinical study personnel to the assigned treatment will continue until the prespecified number of 300 overall survival (OS) events is reached. Patients received study treatment until disease progression, unacceptable toxicity, noncompliance, or investigator or patient decision.

Outcome Measures

The primary end point for the randomized phase 3 portion of RELAY was PFS (time from randomization to disease progression or death from any cause) as evaluated by investigators according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1). Secondary end points included OS, objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and safety.¹⁸ Prespecified exploratory end points included PFS2 (time from randomization to second disease progression or death from any cause, whichever occurred first) and biomarker analyses. Liquid biopsy samples from baseline and poststudy treatment discontinuation (30-d follow-up) were analyzed for treatment-emergent *EGFR* T790M by Guardant360 (Guardant Health, Redwood City, CA) NGS. Time to chemotherapy treatment (TTCT; time from randomization to start of chemotherapy or death) was a post hoc exploratory end point.¹⁸

Statistical Analysis

Details of the RELAY statistical analyses have been published.¹⁸ The analyses in this report were exploratory, and multiplicity was not adjusted. Therefore, only point estimates and CIs are reported, without p values. The data cutoff date was January 23, 2019. Efficacy end points were evaluated in the Japanese intent-to-treat (ITT) population (all randomized patients enrolled in Japan; prespecified analysis). PFS, PFS2, and DoR (for patients achieving a best overall response of partial or complete response) were analyzed using the Kaplan-Meier method and compared using the unstratified log-rank test. ORR

Table 1. Demographic and Clinical Characteristics of Patients at Baseline (Japanese ITT Population)

Characteristics ^a	RAM + ERL (N = 106)	PL + ERL (N = 105)
Sex		
Female	72 (67.9)	68 (64.8)
Age, y		
Median	67	66
Min-max	41-86	35-83
Race		
Asian	106 (100)	105 (100)
Smoking history		
Ever	28 (26.4)	34 (32.4)
Never	63 (59.4)	64 (61.0)
Unknown or missing	15 (14.2)	7 (6.7)
ECOG performance status		
0	59 (55.7)	60 (57.1)
1	47 (44.3)	45 (42.9)
Disease classification		
Primary metastatic	95 (89.6)	94 (89.5)
Recurrent metastatic	11 (10.4)	11 (10.5)
EGFR mutation type ^b		
Ex19del	49 (46.2)	51 (48.6)
Ex21.L858R	56 (52.8)	54 (51.4)
EGFR testing method ^c		
therascreen and cobas	40 (37.7)	42 (40.0)
Other PCR and sequencing-based methods	65 (61.3)	63 (60.0)

^aExcept where otherwise indicated, data are n (%).

^bIn the RAM + ERL arm, 1 patient was classified as other.

^cIn the RAM + ERL arm, 1 patient was classified as missing.

ECOG, Eastern Cooperative Oncology Group; ERL, erlotinib; ex19del, exon 19 deletion; ex21.L858R, exon 21 L858R; ITT, intent-to-treat; Max, maximum; Min, minimum; PCR, polymerase chain reaction; PL, placebo; RAM, ramucirumab.

and DCR were calculated as defined by RECIST v1.1 and compared using the Cochran-Mantel-Haenszel test. HRs and 95% CIs were estimated using unstratified Cox proportional hazards models, which, where applicable, also included an interaction term with treatment for evaluating predictive relationships. Safety end points were evaluated in the Japanese safety population (all patients enrolled in Japan who were treated with ≥ 1 dose of study treatment) as previously described.^{18,24}

Guardant360 NGS T790M analysis subpopulations comprised Japanese ITT patients who had disease progression by data cutoff and NGS results at baseline and at 30-day follow-up (population 1) or NGS results at 30-day follow-up containing an EGFR-activating mutation (population 2), indicating the liquid biopsy contained tumorshed DNA. T790M mutation rates, defined as the proportion of patients with T790M mutation, and associated Wilson score 95% CIs were determined, and the differences in T790M mutation rate between treatment arms at each time point were evaluated using Fisher's exact test.

Results

Patient Disposition and Baseline Demographics

The Japanese ITT population comprised 211 (47.0% of the RELAY global population) patients (RAM + ERL:

106 patients; PL + ERL: 105 patients; [Supplementary Fig. 1](#)) enrolled at 41 sites. One patient in the RAM + ERL arm was randomized but never treated. Median duration of follow-up was 22.4 months (range: 0.4–35.0). At the time of data cutoff, 31 of 106 patients (29.2%) in the RAM + ERL arm and 18 of 105 (17.1%) 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: 48 of 106 [45.3%]; PL + ERL: 62 of 105 [59.0%]) and adverse events (AEs) (RAM + ERL: 17 of 106 [16.0%]; PL + ERL: 22 of 105 [21.0%]). Baseline characteristics were mostly balanced across treatment arms ([Table 1](#)).

Efficacy

In the Japanese ITT population, PFS (investigator-assessed) was longer in the RAM + ERL arm versus the PL + ERL arm ([Fig. 1A](#)). Median (95% CI) PFS was 19.4 (15.2–22.1) versus 11.2 (9.8–13.8) months (HR = 0.610 [95% CI: 0.431–0.864]). The 1-year and 18-month PFS rates were greater in the RAM + ERL arm versus the PL + ERL arm ([Fig. 1A](#)). PFS was improved in the RAM + ERL arm versus the PL + ERL arm in patients with ex19del [16.6 [95% CI: 13.9–30.3] versus 12.5 [95% CI: 9.9–17.9] mo; HR = 0.701

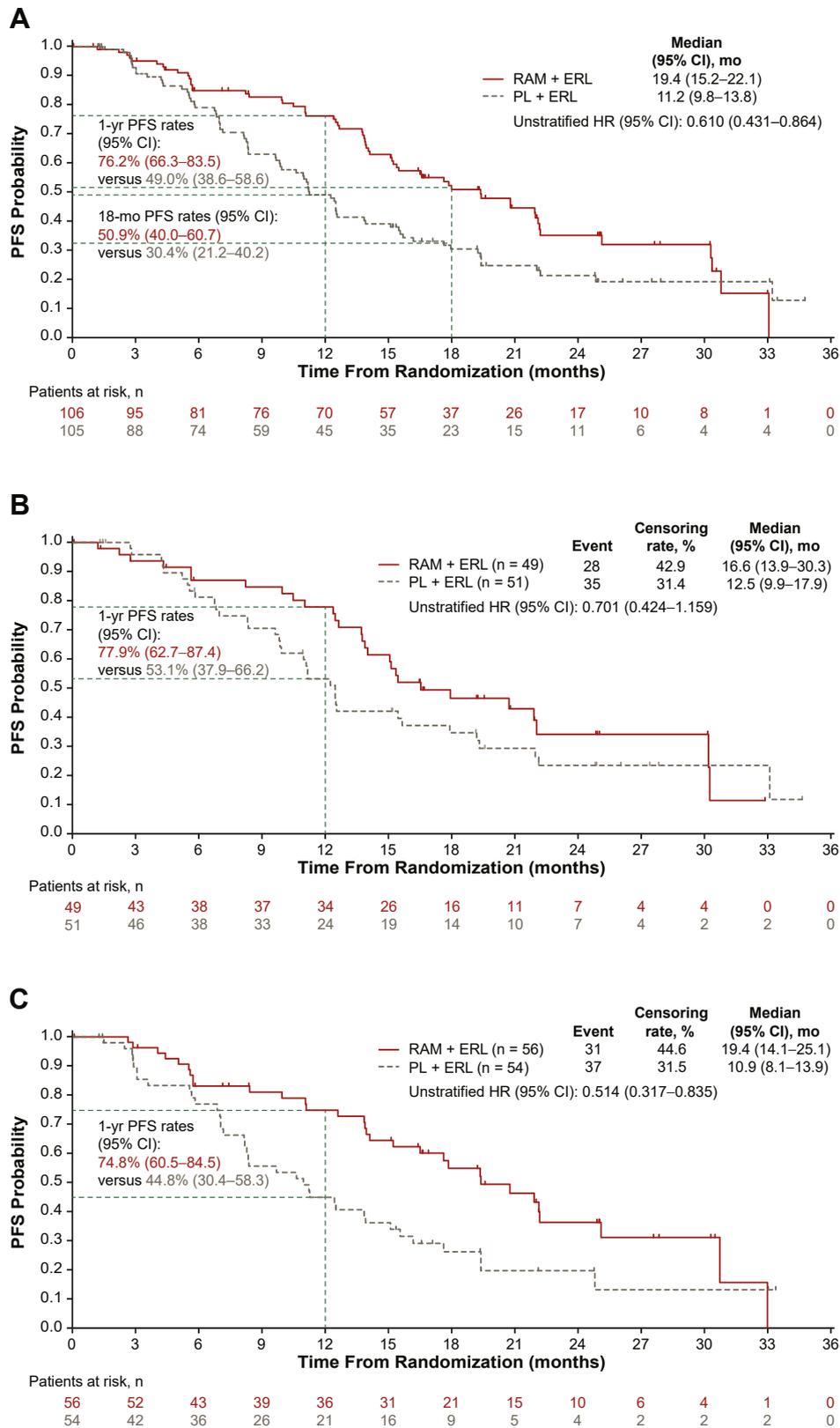


Figure 1. Kaplan-Meier plot of investigator-assessed PFS (Japanese ITT population). (A) All patients in the Japanese ITT population. (B) Patients with EGFR exon 19 deletion at baseline. (C) Patients with EGFR exon 21 L858R mutation at baseline. CI, confidence interval; ERL, erlotinib; HR, hazard ratio; ITT, intent-to-treat; mo, month; PFS, progression-free survival; PL, placebo; RAM, ramucirumab; yr, year.

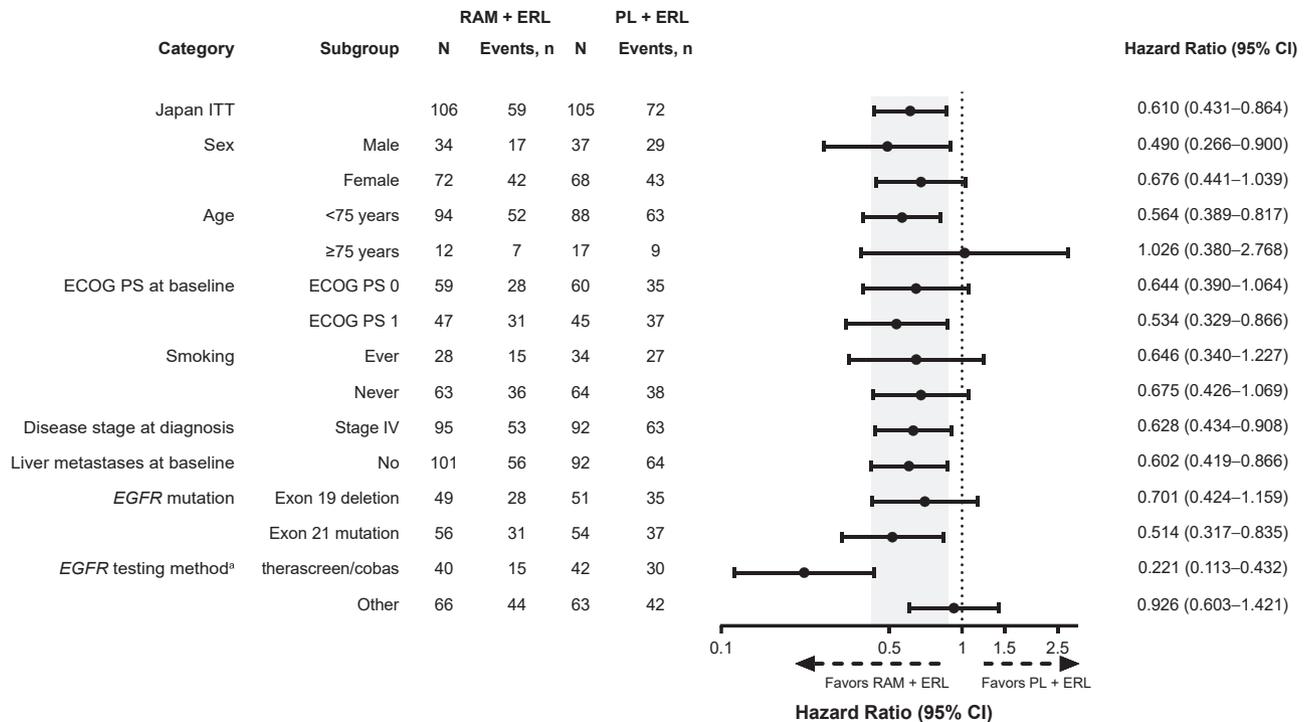


Figure 2. Investigator-assessed PFS subgroup analysis (Japanese ITT population). The following categories with events less than 10 in either treatment arm are not revealed: unknown smoking history, a disease stage of “other” at diagnosis, and liver metastases at baseline. Shaded area represents the 95% CI for the Japan ITT population. ^a96% agreement between pre-planned confirmatory central *EGFR* testing (therascreen assay) and local laboratory results (therascreen, cobas, or other PCR and sequencing-based methods) was observed. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ERL, erlotinib; ITT, intent-to-treat; PCR, polymerase chain reaction; PFS, progression-free survival; PL, placebo; RAM, ramucirumab.

[95% CI: 0.424–1.159]) (Fig. 1B) and in patients with ex21.L858R (19.4 [95% CI: 14.1–25.1] versus 10.9 [95% CI: 8.1–13.9] mo; HR = 0.514 [95% CI: 0.317–0.835]) (Fig. 1C). The PFS benefit of RAM + ERL compared with PL + ERL was consistent across most prespecified patient subgroups (including sex, smoking status, and *EGFR* mutation type), although there is currently no clear explanation for the different HRs for *EGFR* testing method (Fig. 2).

The ORR, DCR, and pattern of best overall response were similar between treatment arms (Table 2 and Fig. 3). In patients who responded, median DoR was longer with RAM + ERL versus PL + ERL (18.0 [95% CI: 12.9–20.9] versus 11.1 [95% CI: 9.0–12.6] mo; HR = 0.585 [0.402–0.850]) (Table 2). At data cutoff, PFS2 and OS data were immature (censoring rates were 67.0% and 86.8% in the RAM + ERL arm and 54.3% and 78.1% in the PL + ERL arm, respectively). HRs (95% CI) for PFS2 and OS were 0.664 (0.430–1.028) (Supplementary Fig. 2) and 0.604 (95% CI: 0.311–1.174), respectively (Table 2). Patients in the RAM + ERL arm had a longer TTCT or death than patients in the PL + ERL arm (median 32.3 versus 23.7 mo; HR = 0.552 [95% CI: 0.363–0.838]) (Supplementary Fig. 3).

Occurrence of Central Nervous System Metastases

A total of 8 of 211 Japanese patients (3.8%) reported central nervous system metastases as a site of disease progression (RAM + ERL: 2 of 106 patients, 1.9%; PL + ERL: 6 of 105 patients, 5.7%).

Treatment Exposure

In the RAM + ERL arm, median (minimum–maximum) duration of exposure (censored analysis excluding 31 patients still on treatment) to RAM was 12.4 months (0.5–33.8+) and to ERL was 15.2 (0.1–33.8+) months; median relative dose intensity for the Japan ITT population was 93.8% and 85.7%, respectively. In the PL + ERL arm, median (minimum–maximum) duration of exposure (censored analysis excluding 18 patients still on treatment) to PL was 8.3 months (0.5–35.4+) and to ERL was 10.7 (0.8–35.5+) months; median relative dose intensity for the Japan ITT population was 95.6% and 79.3%, respectively.

Duration of RAM exposure (censored analysis excluding patients still on treatment) was similar by age group (<75 y; ≥75 y) with dose adjustments in both

Table 2. Secondary Efficacy End Points (Japanese ITT Population)

Variables	RAM + ERL (N = 106)	PL + ERL (N = 105)
Best overall response, n (%)		
Complete response	1 (0.9)	0
Partial response	80 (75.5)	79 (75.2)
Stable disease	20 (18.9)	22 (21.0)
Progressive disease	1 (0.9)	1 (1.0)
Not assessable	4 (3.8)	3 (2.9)
Objective response rate, n	81	79
% (95% CI)	76.4 (68.3-84.5)	75.2 (67.0-83.5)
Disease control rate, n	101	101
% (95% CI)	95.3 (91.2-99.3)	96.2 (92.5-99.9)
Duration of response ^a		
Events	50 (61.7)	62 (78.5)
Median (95% CI), mo	18.0 (12.9-20.9)	11.1 (9.0-12.6)
Unstratified HR (95% CI)	0.585 (0.402-0.850)	
Interim overall survival		
Events	14	23
Censoring rate, %	86.8	78.1
Median (95% CI), mo	Not reached	Not reached
Unstratified HR (95% CI)	0.604 (0.311-1.174)	
Survival rate, % (95% CI)		
12 mo	95.1 (88.7-98.0)	94.3 (87.7-97.4)
18 mo	92.0 (84.6-95.9)	88.4 (80.4-93.2)
Progression-free survival 2 ^b		
Events	35	48
Censoring rate, %	67.0	54.3
Median (95% CI), mo	33.1 (26.48-NA)	28.0 (21.82-NA)
Unstratified HR (95% CI)	0.664 (0.430-1.028)	

^aIn patients who responded (RAM + ERL: n = 81; PL + ERL: n = 79).

^bTime from randomization to second disease progression (defined as objective radiologic or symptomatic progression after start of additional systemic anticancer treatment) or death from any cause, whichever occurred first.

CI, confidence interval; ERL, erlotinib; HR, hazard ratio; ITT, intent-to-treat; NA, not available; PL, placebo; RAM, ramucirumab.

treatment arms. Duration of ERL exposure was longer for patients younger than 75 years versus patients 75 years or older in the PL + ERL arm ([Supplementary Table 1](#) and [Supplementary Fig. 4](#)). Median relative dose intensity of RAM was high and comparable between age groups; median relative dose intensity was lower for ERL ([Supplementary Table 1](#)).

In the RAM + ERL arm, RAM dose adjustments were required for 78 of 105 patients (74.3%); ERL dose adjustments were required for 81 of 105 patients (77.1%) ([Supplementary Table 2](#)). In the PL + ERL arm, PL dose adjustments were required for 64 of 105 patients (61.0%); ERL dose adjustments were required for 71 of 105 patients (67.6%) ([Supplementary Table 2](#)). Dose adjustments for RAM or PL were mainly dose delays (RAM + ERL: 71 of 105 [67.6%]; PL + ERL: 62 of 105 [59.0%]) primarily owing to an AE, most often increased blood bilirubin and alanine aminotransferase. Dose adjustments for ERL were mainly dose omissions (RAM + ERL: 71 of 105 [67.6%]; PL + ERL: 67 of 105 [63.8%]) and dose reductions (RAM + ERL: 56 of 105 [53.3%]; PL + ERL: 53 of 105 [50.5%]). Almost all dose adjustments were due to an AE, most often dermatitis acneiform.

Postdiscontinuation Therapy

Subsequent anticancer therapy after study treatment discontinuation was at the investigator's discretion. With 29.2% versus 17.1% of patients in the RAM + ERL and PL + ERL arms, respectively, remaining on the study treatment at data cutoff, 63 of 106 patients (59.4%) in the RAM + ERL arm and 78 of 105 patients (74.3%) in the PL + ERL arm received 1 or more subsequent lines of anticancer therapy ([Supplementary Table 3](#)). The most common first subsequent line of treatment after study treatment discontinuation was an EGFR TKI (RAM + ERL: 51 of 63 patients [81.0%]; PL + ERL: 58 of 78 patients [74.4%]), with 61.9% (RAM + ERL: 39 of 63 patients) and 41.0% (PL + ERL: 32 of 78 patients) receiving ERL versus 9.5% (RAM + ERL: 6 of 63 patients) and 14.1% (PL + ERL: 11 of 78 patients) receiving osimertinib. Chemotherapy was received by 10 of 63 patients (15.9%) and 18 of 78 patients (23.1%) in the RAM + ERL and PL + ERL arms, respectively. A second subsequent line of therapy after study treatment discontinuation was received by 41 of 106 patients (38.7%) in the RAM + ERL arm

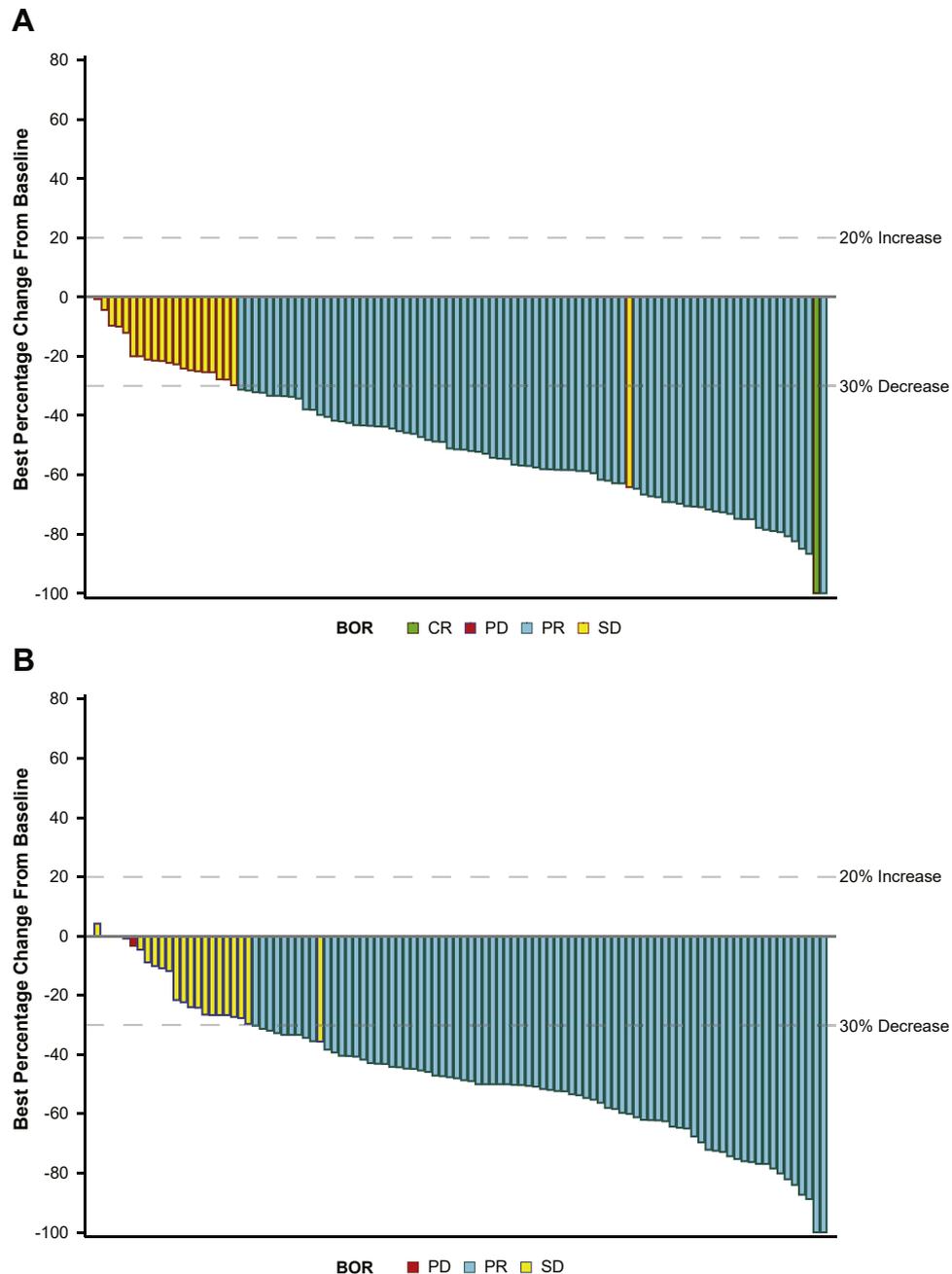


Figure 3. Maximum percentage change from baseline in the sum of all target tumors (Japanese ITT population). (A) RAM + ERL treatment arm. (B) PL + ERL treatment arm. BOR, best overall response; CR, complete response; ERL, erlotinib; ITT, intent-to-treat; PD, progressive disease; PL, placebo; PR, partial response; RAM, ramucirumab; SD, stable disease.

and 47 of 105 patients (44.8%) in the PL + ERL arm. EGFR TKI treatment was received by 24 of 41 patients (58.5%) and 15 of 47 patients (31.9%) in the RAM + ERL and PL + ERL arms, respectively. Osimertinib was the most common EGFR TKI (RAM + ERL: 17 of 41 patients [41.5%]; PL + ERL: 13 of 47 patients [27.7%]). Chemotherapy was received by 17 of 41 patients (41.5%) and 31 of 47 patients (66.0%) in the RAM + ERL and PL + ERL arms, respectively.

Safety

All patients in the Japanese safety population reported at least 1 treatment-emergent AE (TEAE). The most common any-grade TEAEs were dermatitis acneiform (RAM + ERL: 91.4%; PL + ERL: 90.5%) and diarrhea (RAM + ERL: 74.3%; PL + ERL: 73.3%) (Table 3). TEAEs of grade 3 or above were reported by 81 of 105 patients (77.1%) in the RAM + ERL arm and 64 of 105 patients (61.0%) in the PL + ERL arm. Most common

Table 3. TEAEs and AEs of Special Interest for RAM (Japanese Safety Population)

Event	RAM + ERL (N = 105)		PL + ERL (N = 105)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
≥ 1 TEAE	105 (100.0)	81 (77.1)	105 (100.0)	64 (61.0)
TEAEs occurring in >40% of patients treated with RAM + ERL				
Dermatitis acneiform	96 (91.4)	25 (23.8)	95 (90.5)	11 (10.5)
Diarrhea	78 (74.3)	7 (6.7)	77 (73.3)	2 (1.9)
Paronychia	73 (69.5)	7 (6.7)	66 (62.9)	5 (4.8)
Increased ALT	68 (64.8)	14 (13.3)	50 (47.6)	15 (14.3)
Increased AST	66 (62.9)	6 (5.7)	45 (42.9)	8 (7.6)
Stomatitis	59 (56.2)	1 (1.0)	41 (39.0)	2 (1.9)
Hypertension	55 (52.4)	26 (24.8)	17 (16.2)	5 (4.8)
Dry skin	48 (45.7)	1 (1.0)	46 (43.8)	3 (2.9)
Proteinuria	47 (44.8)	3 (2.9)	11 (10.5)	0 (0.0)
Epistaxis	47 (44.8)	0 (0.0)	19 (18.1)	0 (0.0)
Alopecia	45 (42.9)	0 (0.0)	18 (17.1)	0 (0.0)
AEs of special interest ^a				
Bleeding or hemorrhage	66 (62.9)	1 (1.0)	41 (39.0)	2 (1.9)
Epistaxis	47 (44.8)	0 (0.0)	19 (18.1)	0 (0.0)
Hematuria	8 (7.6)	0 (0.0)	6 (5.7)	2 (1.9)
Purpura	8 (7.6)	0 (0.0)	5 (4.8)	0 (0.0)
Gingival bleeding	7 (6.7)	0 (0.0)	1 (1.0)	0 (0.0)
GI hemorrhage ^b	12 (11.4)	1 (1.0)	4 (3.8)	0 (0.0)
Hypertension	55 (52.4)	26 (24.8)	17 (16.2)	5 (4.8)
Proteinuria ^c	48 (45.7)	3 (2.9)	11 (10.5)	0 (0.0)
Liver injury or liver failure and liver infection	86 (81.9)	20 (19.0)	78 (74.3)	22 (21.0)
Increased ALT	68 (64.8)	14 (13.3)	50 (47.6)	15 (14.3)
Increased AST	66 (62.9)	6 (5.7)	45 (42.9)	8 (7.6)
Increased blood bilirubin	40 (38.1)	2 (1.9)	43 (41.0)	0 (0.0)
Increased GGT	7 (6.7)	2 (1.9)	6 (5.7)	0 (0.0)
Abnormal hepatic function	7 (6.7)	4 (3.8)	6 (5.7)	3 (2.9)
Infusion-related reactions	2 (1.9)	0 (0.0)	1 (1.0)	0 (0.0)
Other TEAE of interest				
ILD	1 (1.0)	1 (1.0)	3 (2.9)	2 (1.9)
Pneumonitis	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)

Note: Data are n (%).

^aAEs of special interest are prespecified selected AEs of clinical interest that have been associated with other antiangiogenic agents, in a similar pharmacologic class as ramucirumab, that inhibit the VEGF signaling pathway.

^bIncludes the preferred terms hemorrhoidal hemorrhage, anal hemorrhage, small intestinal hemorrhage, lower gastrointestinal hemorrhage, and hematochezia.

^cIncludes the preferred terms proteinuria and protein urine present.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERL, erlotinib; GGT, gamma-glutamyltransferase; GI, gastrointestinal; ILD, interstitial lung disease; PL, placebo; RAM, ramucirumab; TEAE, treatment-emergent adverse event; VEGF, vascular endothelial growth factor.

TEAEs of grade 3 or above were hypertension (24.8%, all grade 3) and dermatitis acneiform (23.8%) in the RAM + ERL arm and increased alanine aminotransferase (14.3%) and dermatitis acneiform (10.5%) in the PL + ERL arm (Table 3). AEs of special interest for antiangiogenic agents included any-grade bleeding or hemorrhage (62.9% versus 39.0%), hypertension (52.4% versus 16.2%), and proteinuria (45.7% versus 10.5%) in the RAM + ERL versus PL + ERL arm, respectively (Table 3). Interstitial lung disease (ILD) was reported in both arms (RAM + ERL: 1 patient, grade 3; PL + ERL: 3 patients, grades 1, 3, and 5; the patient with grade 5 ILD died from ILD after study treatment discontinuation). The incidence of treatment-emergent serious AEs was

similar across treatment arms: 25 of 105 patients (23.8%) for RAM + ERL versus 28 of 105 patients (26.7%) for PL + ERL. No patient in the Japanese safety population died while on study treatment.

The frequency of TEAEs of grade 3 or above in patients aged 75 years or older was higher than in patients younger than 75 years (RAM + ERL: 10 of 12 patients [83.3%] versus 71 of 93 patients [76.3%]; PL + ERL: 12 of 17 patients [70.6%] versus 52 of 88 patients [59.1%]) (Supplementary Table 4). Common TEAEs of any grade with RAM + ERL treatment were similar between age groups but occurred less frequently in patients aged 75 years or older, except for any-grade proteinuria, which occurred in 50.0% of patients aged 75 years or older and

44.1% in those younger than 75 years (Supplementary Table 4). Discontinuation of all study treatment owing to an AE or serious AE occurred in 3 of 12 patients (25.0%) and 2 of 12 patients (16.7%) aged 75 years or older, respectively, in the RAM + ERL arm, and 14 of 93 patients (15.1%) and 3 of 93 patients (3.2%) in the PL + ERL arm.

Treatment-Emergent T790M Rates

Postprogression T790M rates for Japanese patients were similar in the RAM + ERL and PL + ERL arms (population 1: RAM + ERL: 25% [95% CI: 14–41], 9 of 36 patients; PL + ERL: 34% [95% CI: 23–47], 20 of 59 patients; population 2: RAM + ERL: 47% [95% CI: 27–68], 9 of 19 patients; PL + ERL: 50% [95% CI: 35–65], 20 of 40 patients) (Supplementary Fig. 5). Postprogression T790M rates were evaluated according to the number of treatment cycles received before the 30-day follow-up visit (Supplementary Fig. 6).

Discussion

In this prespecified subset analysis of RELAY Japanese patients with previously untreated metastatic *EGFR*-mutated NSCLC, the safety and clinically meaningful efficacy of RAM + ERL versus PL + ERL was confirmed. The primary efficacy end point (PFS) was improved with RAM + ERL versus PL + ERL (19.4 versus 11.2 mo; HR = 0.610 [95% CI: 0.431–0.864]). The PFS benefit was consistent for ex19del and ex21.L858R and other prespecified subgroups in the Japanese population. Clinical benefit with RAM + ERL was confirmed in secondary (DoR) and exploratory (TTCT) end points, with a manageable safety profile. This subset analysis suggests that RAM + ERL is an effective and safe treatment option for *EGFR*-mutated NSCLC in Japanese patients.

Despite initial benefits, early generation *EGFR* TKIs are associated with the development of treatment resistance and loss of clinical benefit. Osimertinib has efficacy and tolerability advantages over these earlier *EGFR* TKIs. In the phase 3 double-blind FLAURA study in patients with *EGFR*-mutated NSCLC, median PFS was significantly improved with first-line osimertinib versus gefitinib or ERL therapy (18.9 versus 10.2 mo; HR = 0.46 [95% CI: 0.37–0.57], $p < 0.001$),²⁵ and PFS in the Japanese subset population was 19.1 months with osimertinib versus 13.8 months with gefitinib (HR = 0.61 [95% CI: 0.38–0.99]).²⁶ Nevertheless, the mechanisms of resistance after first-line osimertinib are heterogeneous and mostly nontargetable. Thus, chemotherapy-based regimens are the only option once patients progress on osimertinib. RELAY was the first global, phase 3, randomized, double-blind, PL-controlled study to reveal

improved median PFS with antiangiogenic plus *EGFR* TKI combination therapy,^{18,24} confirming the results obtained in the randomized phase 2 (JO25567) and phase 3 (NEJ026) Japanese open-label studies of bevacizumab plus ERL.^{17,27} In this RELAY Japanese subset, PFS was longer and TTCT was delayed for patients receiving RAM + ERL compared with patients receiving PL + ERL. Furthermore, the rates of postprogression T790M acquisition were similar across treatment arms (population 2: 47% [RAM + ERL] versus 50% [PL + ERL]) and similar to the RELAY global and East Asian populations.^{18,24} The cumulative incidence of T790M across increasing numbers of treatment cycles received before progression suggests that RAM + ERL might delay the emergence of this resistance mechanism; however, the sample size was limited. T790M is a resistance mechanism for which effective targeted treatment, that is, osimertinib, is available. In the phase 3 AURA3 study, median PFS was significantly longer with osimertinib than with platinum therapy plus pemetrexed (10.1 versus 4.4 mo, respectively; HR = 0.30, 95% CI: 0.23–0.41, $p < 0.001$) in patients with T790M-positive advanced NSCLC in whom disease had progressed during first-line *EGFR* TKI therapy.²⁸ These results suggest that for patients with NSCLC who acquire the T790M mutation, treatment sequence could comprise first-line *EGFR* TKI plus antiangiogenic therapy, second-line osimertinib, and then chemotherapy. The results of the RELAY global study, and the East Asian and Japanese subset analyses, reveal that antiangiogenic plus *EGFR* TKI combination therapy is a viable first-line treatment strategy for patients with NSCLC with *EGFR* mutations.^{18,24}

Preclinical studies revealed that *EGFR*-activating mutations have differential sensitivity to *EGFR* TKIs.^{5,6} In a meta-analysis of 12 trials, patients with NSCLC with ex19del mutation had longer PFS and OS, and higher response rates, with *EGFR* TKI therapy than patients with ex21.L858R mutation.⁸ In the RELAY global ITT population, PFS benefit with RAM + ERL treatment was similar for both *EGFR* mutation subgroups (median [95% CI] PFS: ex21.L858R: 19.4 [14.1–21.9] mo; HR [95% CI]: 0.62 [0.44–0.87]; ex19del, 19.6 [15.1–22.2] mo; HR: 0.65 [0.47–0.90]).¹⁸ A PFS benefit for ex21.L858R patients with RAM + ERL treatment was also observed in the RELAY Japanese population (median [95% CI] PFS: ex21.L858R: 19.4 [14.1–25.1] mo; unstratified HR = 0.514 [0.317–0.835]; ex19del: 16.6 [13.9–30.3] mo; unstratified HR = 0.701 [0.424–1.159]).

Japanese patients are at risk of developing ILD, a known complication of *EGFR* TKI therapy.²⁹ The incidence rate of ILD or pneumonitis with *EGFR* TKI treatment in Japanese patients with NSCLC has been reported

to be 12.3% with osimertinib and 1.8% with gefitinib.²⁶ In NEJ026, no ILD events were reported with bevacizumab plus ERL versus 4% of patients with ERL monotherapy.²⁷ The incidence of ILD or pneumonitis with RAM + ERL in both the RELAY global and Japanese populations was low (1.0%–1.8%) versus PL + ERL (2.7%–4.8%).¹⁸ This is an important finding for Japanese patients because EGFR TKI treatment cannot continue in patients who develop ILD.

Because the Japanese subset analysis was not powered to reveal differences between RAM + ERL and PL + ERL, the results need to be interpreted with caution, although the results do align with those of the global RELAY study.¹⁸ In addition, the exploratory analysis of *EGFR* T790M rates was limited to patients with both a baseline and a 30-day follow-up NGS sample, or to those with an *EGFR*-activating mutation detected in the post-progression 30-day follow-up sample, which further reduced the sample size.

In conclusion, RELAY revealed a favorable benefit-risk profile for RAM + ERL in the first-line treatment of Japanese patients with *EGFR*-mutated NSCLC, consistent with the global RELAY population. Liquid biopsy analyses indicated that the addition of RAM did not affect the ERL-associated *EGFR* T790M rates at disease progression.

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Data Sharing Statement

Eli 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 months 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, and 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.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at <https://doi.org/10.1016/j.jtocrr.2021.100171>.

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