ORIGINAL ARTICLE

RELAY: Final Overall Survival for Erlotinib Plus Ramucirumab or Placebo in Untreated, *EGFR*-Mutated Metastatic NSCLC

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ABSTRACT

Introduction: RELAY, a global double-blind, placebo-controlled phase 3 study (NCT02411448) found statistically significant improvement in progression-free survival (primary end point) for ramucirumab (RAM) plus erlotinib (ERL) (RAM + ERL) in patients with untreated *EGFR*-mutated metastatic NSCLC (hazard ratio [HR] = 0.59, 95% confidence interval [CI]: 0.46–0.76, $p < 0.0001$; median progression-free survival: 19.4 versus 12.4 mo). Here, we report the final overall survival (OS; secondary end point) outcomes for the intention-to-treat population.

Methods: Between January 2016 and February 2018, 449 eligible patients with an *EGFR* exon 19del or L858R

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A Study of Ramucirumab (LY3009806) in Combination With Erlotinib in Previously Untreated Participants With EGFR Mutation-Positive Metastatic NSCLC (RELAY).

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mutation and no central nervous system metastases were randomized (1:1) to ERL (150 mg/day) with RAM (10 mg/kg every two weeks, N = 224) or placebo (N = 225).

Results: At data cutoff, 297 deaths were reported (overall event rate = 66%), with a median follow-up of 45.1 months (interquartile range: 26.7–71.2), an OS HR of 0.98 (95% CI: 0.78–1.24, $p = 0.864$), and median OS of 51.1 months (RAM + ERL) and 46.0 months (placebo + ERL). Outcomes in subsets of patients with poor prognosis (L858R or *TP53* co-mutation) suggest a directional improvement in OS (L858R: HR = 0.87, 95% CI: 0.62–1.22; exon 19del: HR = 1.13, 95% CI: 0.83–1.55; *TP53* co-mutation: HR = 0.83, 95% CI: 0.58–1.19; *TP53*-wild-type: HR = 1.22, 95% CI: 0.87–1.72). Treatment-emergent T790M rates were similar between arms. Over 80% of patients received post-study discontinuation therapy (>50% received osimertinib in comparable numbers between arms). The safety profile for RAM + ERL was consistent with previous reports with no increased toxicity over time or new safety signals observed.

Conclusion: In RELAY, OS was not significantly improved with similar long OS durations in both treatment arms.

Clinical Trial Information: ClinicalTrials.gov Identifier: NCT02411448

Keywords: NSCLC; *EGFR* mutation; Ramucirumab; Erlotinib; Overall survival

Introduction

EGFR–tyrosine kinase inhibitors (TKIs) are recommended as first-line (1L) therapy for patients with *EGFR*-mutated NSCLC. Nevertheless, not all patients benefit equally from treatment with EGFR-TKIs suggesting that factors other than *EGFR* mutation may affect outcomes to EGFR-TKIs.[1–3] Although response rates with EGFR-TKIs are as high as 80%, response duration may be limited, and resistance to treatment and disease progression is inevitable.[4,5] This has led to the evaluation of upfront combination therapy strategies with the intent to improve outcomes further.[6]

One such strategy supported by preclinical and clinical evidence is the dual blockade of the EGFR and vascular endothelial growth factor (VEGF) pathways.[7–11] In the RELAY trial (NCT02411448), erlotinib (ERL), a first-generation TKI was combined with ramucirumab (RAM), a human IgG1 VEGFR2 antagonist, or placebo (PBO), in patients with untreated *EGFR*-mutated metastatic NSCLC. RELAY met its primary end point by demonstrating a statistically significant improvement in progression-free survival (PFS) with a hazard ratio [HR] of 0.59 (95% confidence interval [CI]: 0.46–0.76), a p value of less than 0.0001 and a median PFS of 19.4 months for RAM plus ERL (RAM + ERL) versus 12.4 months for PBO plus ERL (PBO + ERL).[9] This was the basis for worldwide approval of the RELAY regimen. At the time of the primary analysis data cutoff, interim survival data were immature (event rate = 18%). Here we report the results of the planned final analysis of overall survival (OS).

Methods

Full details of RELAY, a global, randomized, double-blind, PBO-controlled, phase 3 trial (ClinicalTrials.gov identifier: NCT02411448), including the design and methods, have been published previously.[9]

Patients, Study Design, and Treatment

Key eligibility criteria included previously untreated stage IV NSCLC (defined by American Joint Committee on Cancer Staging criteria seventh edition, 2009), documented *EGFR* exon 19 deletions (exon 19del) or exon 21 (L858R) mutations, Eastern Cooperative Oncology Group performance score 0 to 1 and measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1. Patients with central nervous system (CNS) metastasis or a known *EGFR* T790M mutation were excluded.

Patients were randomized (1:1) to receive either RAM 10 mg/kg or PBO intravenously once every two weeks and oral ERL 150 mg/day until disease progression, unacceptable toxicity, or another reason for study discontinuation was met. Patients were stratified according to geographic region (East Asia versus Other), sex, *EGFR* mutation subtype (exon 19del versus L858R), and *EGFR* testing method (Therascreen or Cobas versus Other). 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. Physicians, patients, site study personnel, and all sponsor personnel in direct contact with sites were blinded to assigned treatment until after the final OS analysis.

End Points

The primary end point of RELAY was PFS. The study was not powered for OS, which was a secondary end point. Other secondary end points included safety and toxicity, overall response (complete and partial response), disease control (complete and partial response plus stable

disease), and duration of response (DOR) (time from first documented response to the date of objective progression or the date of death, whichever is earlier). Prespecified exploratory end points were biomarker analyses and time to diagnosis of CNS metastases (defined as the time from randomization to CNS metastases).

Statistical Methods

The final OS analysis was planned when approximately 300 deaths were reported. OS was defined as the time from the date of randomization to the date of death from any cause. OS was censored for the last date the patient was known to be alive (on or before the data cut-off date). Assessments for survival were made every three months after disease progression until death or study completion, whichever occurs first.

Kaplan-Meier method was used with a stratified log-rank test to compare OS between treatment arms. The analysis was stratified by the randomization strata. HRs for the treatment effect and associated CIs (95% CIs) were estimated using a Cox proportional hazards model. An unstratified Cox proportional hazards model was used to analyze prespecified subgroups to assess the internal consistency of study results. Results were displayed graphically using Kaplan-Meier plots and a Forest plot. Adverse events were graded with the use of the National Cancer Institute–Common Terminology Criteria for Adverse Events version 4.0. Descriptive statistics for treatment-emergent adverse events (TEAEs) were summarized by the study treatment arm. Liquid biopsy for detection of biomarkers including T790M mutations by Guardant360 next-generation sequencing (NGS) was taken at baseline and 30-day post-study treatment discontinuation (PDT) follow-up. Fisher's exact test was used to compare the difference in T790M mutation frequency between arms.

All efficacy end points were assessed in the intention-to-treat population (ITT), which included all randomly assigned patients. Observed data were used and missing data were not imputed or carried forward. Safety was assessed in all randomized patients who received at least one dose of any study treatment (safety population). T790M analyses were done in the subset of ITT patients who had disease progression by data cutoff and had available NGS results.

Results

Demographics

Between January 28, 2016, and February 1, 2018, 449 patients across 100 sites in 13 countries were enrolled (ITT population). Patients were randomly assigned to either RAM + ERL (N = 224) or PBO + ERL (N = 225; Supplementary Fig. 1). Baseline characteristics were balanced between treatment arms and generally reflective of an *EGFR*-mutated metastatic NSCLC population as previously described.[9] Key details can be viewed in the supplemental appendix (Supplementary Table 1). At the final data cut-off (October 20, 2023), the median duration of follow-up was 45.1 months (interquartile range [IQR]: 26.7–71.2).

PFS

The primary end point of PFS has previously been disclosed.[9] PFS was re-assessed and benefit was sustained at data cutoff for final OS analysis (stratified HR = 0.66, 95% CI: 0.53–0.83, $p = 0.0002$, median PFS: 19.6 versus 12.4 mo), with the following PFS landmarks: 72.0% versus 50.9% at 12 months, 54.2% versus 34.7% at 18 months, and 33.4% versus 22.6% at 24 months for RAM + ERL versus PBO + ERL, respectively (Supplementary Fig. 2).

The unstratified DOR HR was 0.71 (95% CI: 0.57–0.89), median DOR was 18.0 months for RAM + ERL and 11.1 months for PBO + ERL with the following DOR landmarks: 66.9% versus 44.1% at 12 months, 28.5% versus 14.5% at 24 months, and 15.5% versus 9.5% at 36 months for RAM + ERL versus PBO + ERL, respectively.

Overall Survival

At the time of the final data cutoff, 297 deaths were reported (RAM + ERL: 148 deaths, PBO + ERL: 149 deaths, overall event rate: 66%), representing the planned number of events and data maturity. The stratified OS HR was 0.98 (95% CI: 0.78–1.24, $p = 0.864$), median OS (mOS) was 51.1 months (95% CI: 44.9–57.3) for RAM + ERL and 46.0 months (95% CI: 43.6–53.0) for PBO + ERL (Fig. 1).

Figure 2 displays the Forest plot for OS for all prespecified subgroups. The OS observed with RAM + ERL compared with PBO + ERL was generally consistent across most predefined subgroups, with varying magnitudes of effect size and overlapping CIs within and across all subgroups. For the subgroups of patients by *EGFR* mutation subtype, OS outcomes for RAM + ERL versus PBO + ERL suggest a directional improvement in patients with a L858R (HR = 0.87, 95% CI: 0.62–1.22, mOS: 51.6 mo for RAM + ERL and 45.8 mo for PBO + ERL) but not in those with an exon 19del (HR = 1.13, 95% CI: 0.83–1.55, mOS: 49.0 mo for RAM + ERL and 51.4 mo for PBO + ERL) (Supplementary Fig. 3).

Clinical Patterns of Disease Progression

Sites of disease progression were recorded in 169 (75.4%) of RAM + ERL patients and 192 (85.3%) of PBO + ERL patients. Of these, 126 patients (56.3%, RAM + ERL) and 138 patients (61.3%, PBO + ERL) presented with single-site progression, and 43 patients

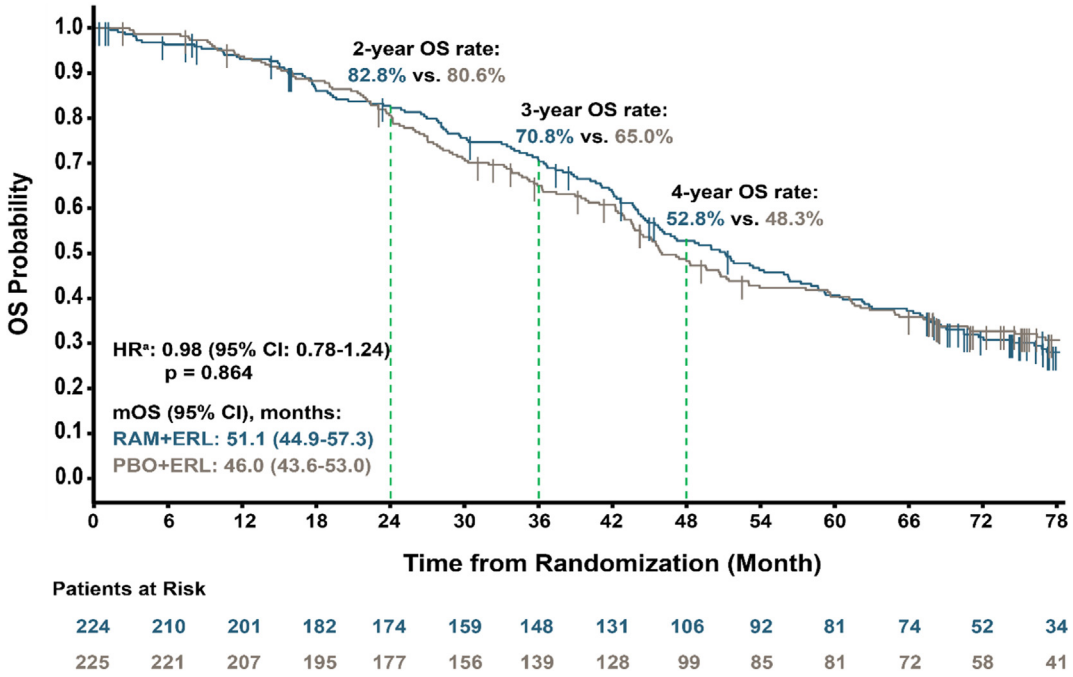


Figure 1. Kaplan-Meier estimates of final OS. The maximum data collection time was 92 months. The figure has been cropped. [a]Stratified HR. HR, hazard ratio; mOS, median OS; OS, overall survival; PBO + ERL, placebo + erlotinib; RAM + ERL, ramucirumab + erlotinib.

(19.2%) and 54 patients (24.0%) presented with multiple-site progression. Brain imaging was performed at baseline, and as clinically indicated during the course of the study. Therefore, the incidence of brain metastases may have been underestimated. Treatment-emergent CNS metastases events were lower in the RAM + ERL arm (3/224; 1.3%) than in the PBO + ERL arm (9/225; 4.0%). Owing to the low number of CNS events, no further analysis was conducted. Similar trends were observed for sites of progression by *EGFR* mutation subtype (Supplementary Table 2).

Post-discontinuation Therapies

More than 80% of patients received PDT (186 patients [83%] in the RAM + ERL arm and 207 patients [92%] in the PBO + ERL arm). The median number of lines of PDT was three (range: 1–10) and two (range: 1–12) for RAM + ERL and PBO + ERL, respectively, with majority of the patients receiving an EGFR-TKI as the first PDT (72.3% RAM + ERL, 78.2% PBO + ERL) (Supplementary Table 3). The high use of ERL as PDT can be explained by the RELAY protocol requirement to discontinue all study treatment at the time of Response Evaluation Criteria in Solid Tumors defined progression (Supplementary Table 4).

Overall, approximately 60% of patients received chemotherapy as PDT with comparable numbers across treatment arms. The post hoc exploratory analysis of time to chemotherapy or death (Supplementary Fig. 4) reported an unstratified HR of 0.97 (95% CI: 0.79–1.19) and a median time to chemotherapy or death of 33.1 months (95% CI: 28.6–36.4) for RAM + ERL and 25.3 months (95% CI: 20.7–30.1) for PBO + ERL. More than 50% of patients received osimertinib as PDT with comparable numbers across treatment arms. The median duration of osimertinib treatment, regardless of line of therapy, was 15.6 (IQR: 6.9–27.5) and 19.3 months (IQR: 9.2–34.9) for RAM + ERL and PBO + ERL patient arms, respectively.

For the patients who did not receive osimertinib post-progression, at any line of treatment, the unstratified OS HR was 0.87 (95% CI: 0.62–1.22) and mOS was 36.7 months (95% CI: 28.3–46.7) and 30.3 months (95% CI: 26.4-40.9) for RAM + ERL and PBO + ERL, respectively. For the patients who did receive osimertinib, post-progression, unstratified OS HR was 1.13 (95% CI: 0.83–1.54) and mOS was 57.3 months (95% CI: 51.2–63.0) for RAM + ERL and 61.3 months (95% CI: 47.4–70.8) for PBO + ERL. A detailed listing of PDT can be found in the supplemental appendix (Supplementary Tables 3 and 4).

Circulating Tumor DNA Analysis

For baseline co-mutation profiles, Guardant360 NGS analyses, from central testing of liquid biopsies, were conducted on circulating tumor DNA (ctDNA) of patients (N = 449) from whom a valid baseline result (passed

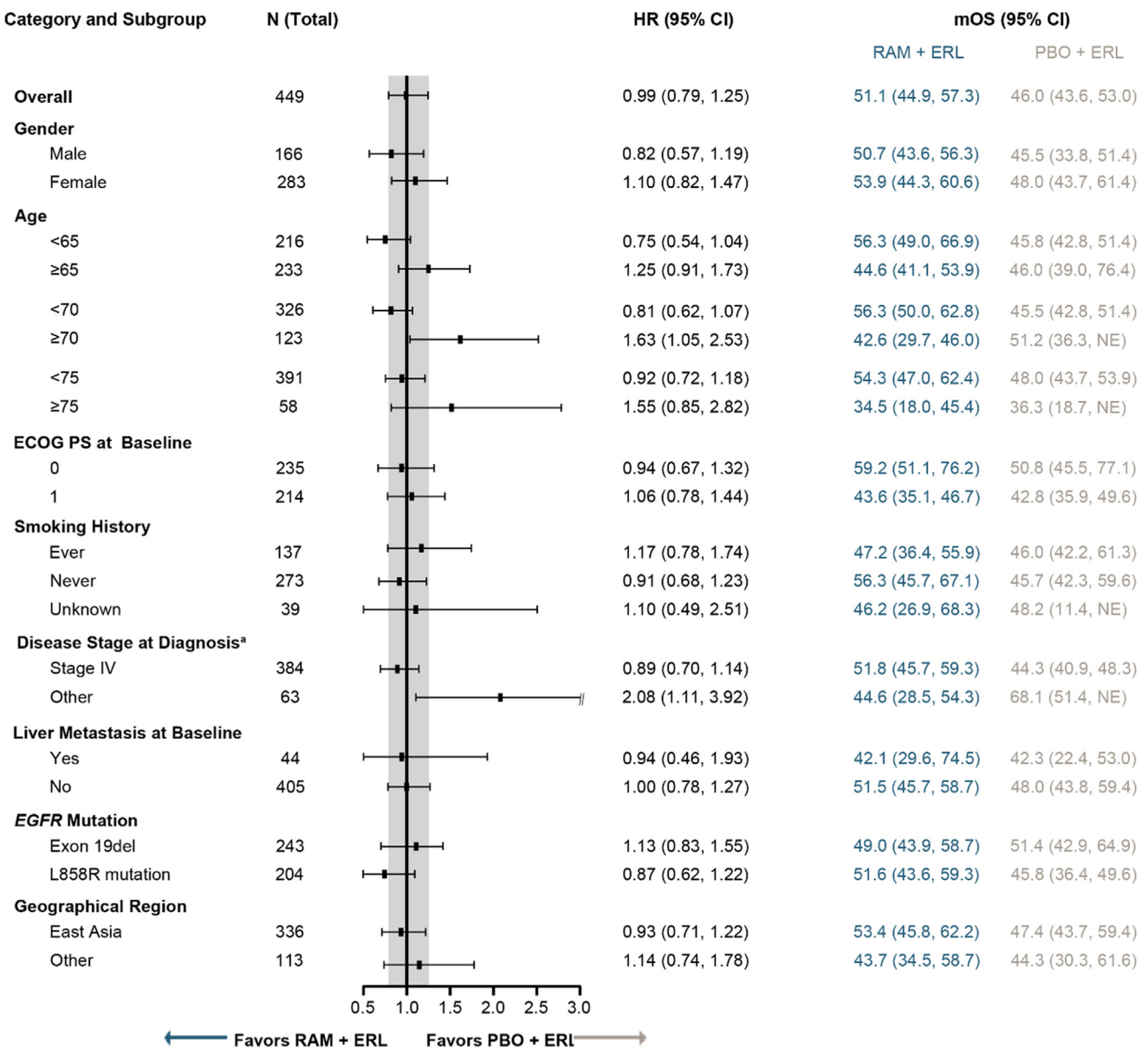


Figure 2. Forest Plot for unstratified subgroup analysis of overall survival. [a]At study entry, all patients had metastatic or stage IV NSCLC. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; PBO + ERL, placebo + erlotinib; RAM + ERL, ramucirumab + erlotinib.

NGS testing quality control) with at least one gene alteration was obtained (n = 386, 86%). Among the 360 patients who had disease progression by data cutoff, valid NGS results were available for 315 patients (88%) at baseline and for 240 patients (67%) at 30-day follow-up.

T790M Resistance Analysis

The most common mechanism of resistance to first- and second-generation EGFR-TKIs is the acquisition of the *EGFR* T790M gatekeeper mutation.[12] Figure 3 shows rates of post-progression T790M from 30-day follow-up samples by treatment arm. Given that different criteria are applied in the literature to define the population for this type of analysis, two approaches are presented. The first analysis (population 1) includes the population of patients who had central liquid biopsy NGS results. Patients who had NGS results at 30-day follow-up, but no NGS results available at baseline were excluded from the analysis. Treatment-emergent T790M rates are similar between the arms (29% RAM + ERL and 29% PBO + ERL). Many tumors do not shed ctDNA into the blood, and the quantity of ctDNA seems to be related to the tumor burden.[13] The second analysis (population 2) includes only those patients for whom an activating *EGFR*

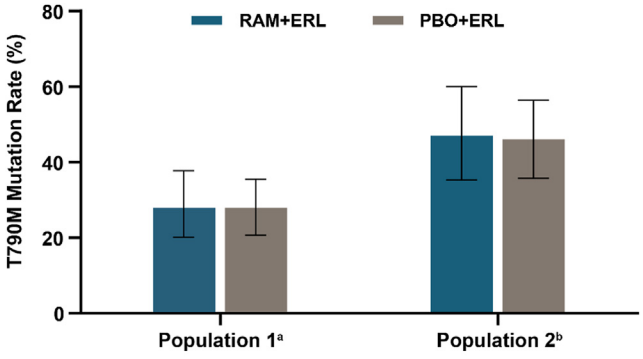
mutation (exon 19del or L8585R) was detected in the 30-day follow-up sample, thereby indicating that the patient's tumor was shedding DNA and suggesting that the liquid biopsy is also likely to detect T790M if it is present in the tumor. This analysis also found similar T790M rates between arms (47% RAM + ERL and 46% PBO + ERL).

TP53 Analysis

At baseline, mutated *TP53* was detected in 42.7% (n = 74 RAM + ERL, n = 91 PBO + ERL) of patients, wild-type *TP53* in 57.3% (n = 118 RAM + ERL, n = 103 PBO + ERL) of patients. Irrespective of treatment, patients with a concurrent *TP53* mutation had poorer OS outcomes in comparison to patients with *TP53*-wild-type tumors, indicating the prognostic impact of a *TP53* comutation (HR = 1.74, 95% CI: 1.36–2.22, mOS: 42.1 and 60.4 mo, respectively). OS outcomes for RAM + ERL versus PBO + ERL suggest a directional improvement in the subset of poorer prognosis patients with *TP53* mutation (HR = 0.83, 95% CI: 0.58–1.19), but not in the more favorable prognosis patients with wild-type *TP53* (HR = 1.22, 95% CI: 0.87–1.72) (Fig. 4).

Safety

The median duration of exposure to RAM or PBO was 11.0 months (4.2–17.6) for RAM + ERL versus 9.7 months (3.7–16.3) for PBO + ERL. The median duration of exposure to ERL was 15.1 months (0.0–82.8) for RAM + ERL versus 11.2 months (0.4–90.4) for PBO + ERL. Dose reductions of RAM or PBO due to TEAEs occurred in 26/221 (11.8%) versus 4/225 (1.8%) patients. Proteinuria was the most common reason for dose reductions of RAM in 21 (9.5%) RAM + ERL patients, with no PBO dose reductions due to proteinuria in PBO + ERL patients. Thirty-six patients (16.3%) in the RAM + ERL arm and 25 patients (11.1%) in the PBO + ERL arm discontinued all study treatment because of TEAEs. The most common TEAE leading to discontinuation was increased alanine aminotransferase. The relative dose intensity was high (>92%) in both treatment arms. At the time of OS analysis, the safety profile of RAM + ERL was consistent with the safety profile in the primary PFS analysis (Supplementary Table 5).[9,12] All patients in the two treatment arms had at least one TEAE (Table 1; Fig. 5). Adverse events of Grade 3 or higher were reported in 76.0% of the patients in the RAM + ERL arm and 56.4% of those in the PBO + ERL arm (Table 1). The difference between the two treatment arms was predominantly due to the higher rate of Grade 3 events in the RAM + ERL treatment arm than the PBO + ERL treatment arm (67.4% and 51.6%, respectively). Grade 3 hypertension, reported in 24% of patients was the largest contributor to Grade 3 or higher TEAEs in the RAM + ERL treatment arm. More than a 5% difference in Grade 3 TEAEs between RAM + ERL and PBO + ERL arms was reported for hypertension (24% and 5.8%), diarrhea (7.2% and 1.3%), and dermatitis acneiform (16.3% and 9.3%). TEAEs reported in 20% or more of patients can be found in Supplementary Table 6. The incidence of Grade 4 TEAEs was similar between the treatment arms (RAM + ERL: 5.4%, PBO + ERL: 4.4%). The most commonly reported



30-day follow-up NGS Data

	RAM+ERL	PBO+ERL	RAM+ERL	PBO+ERL
n:	26/89	36/126	28/59	39/85
% rate:	29%	29%	47%	46%
95% CI:	20.8-39.4	21.4-37.0	35.3-60.0	35.7-56.4
p-value	>0.999		>0.867	

Figure 3. Post-progression *EGFR* T790M rates from the 30-day follow-up liquid biopsy sample. [a]There were 25 patients with post-progression 30-day follow-up NGS results who did not have corresponding baseline NGS results. [b]There were 96 patients with post-progression 30-day follow-up NGS results in whom EGFR activating mutations could not be detected. CI, confidence interval; n, number of patients in a specific group; NGS, next-generation sequencing; PBO + ERL, placebo + erlotinib; RAM + ERL, ramucirumab + erlotinib.

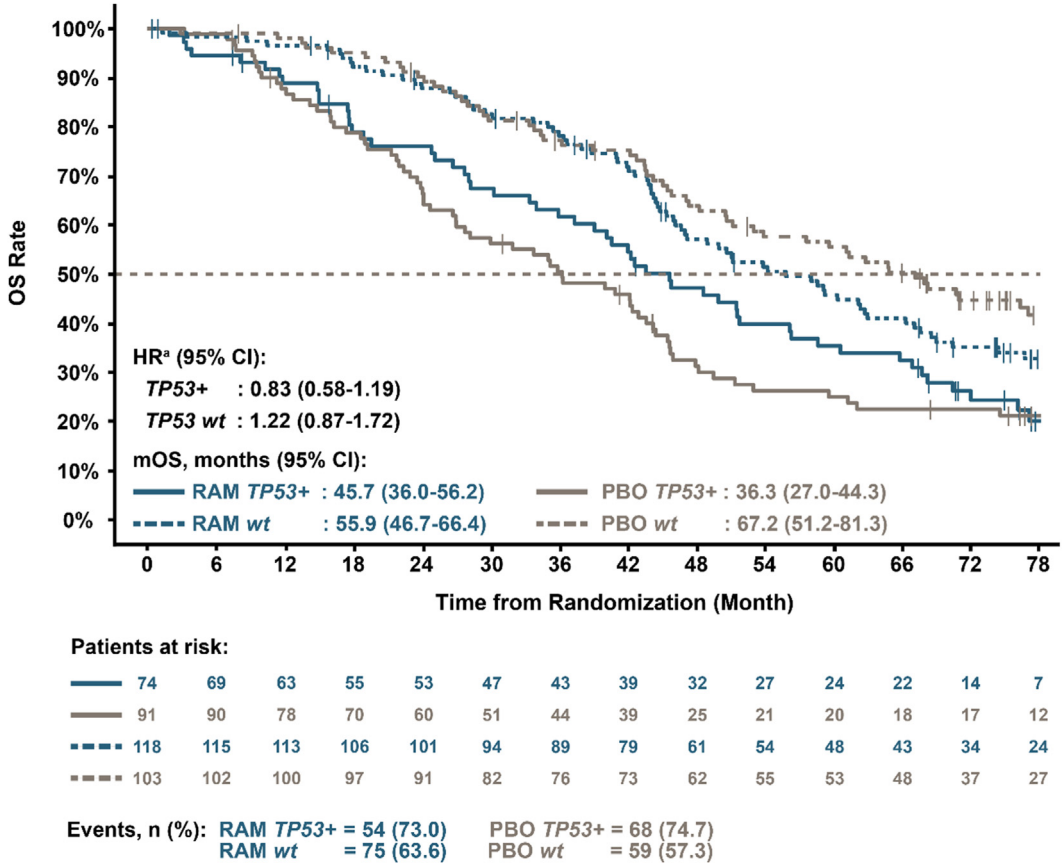


Figure 4. Kaplan-Meier estimates of overall survival by *TP53* co-mutation status at baseline. The maximum data collection time was 92 months. The figure has been cropped. [a]Unstratified HR. CI, confidence interval; HR, hazard ratio; PBO + ERL, placebo + erlotinib; RAM + ERL, ramucirumab + erlotinib; *TP53*+, *TP53*-mutated; wt, wild-type.

Grade 4 TEAEs (alanine aminotransferase increased and hepatic function abnormal) remained the same as previously reported.[9] One additional fatal TEAE of sudden death was reported for RAM + ERL since the primary database lock.

Serious adverse events were reported in 32.6% and 22.7% of patients treated with RAM + ERL or PBO + ERL respectively, indicating a non-notable change in serious adverse events compared with the primary analysis despite longer treatment durations.[9]

Discussion

RELAY, the global phase 3 study in untreated *EGFR*-mutated NSCLC, had met its primary end point by demonstrating a statistically significant and clinically meaningful improvement in PFS (HR = 0.59, 95% CI: 0.46–0.76, $p < 0.0001$, mPFS: 19.4 mo for RAM + ERL versus 12.4 mo for PBO + ERL), which was the basis for world-wide regulatory approval of the RELAY regimen. At data cutoff for final OS analysis, the previously reported PFS benefit of seven months in favor of RAM + ERL was sustained (HR = 0.66, 95% CI: 0.53–0.83, $p = 0.0002$, mPFS: 19.6 versus 12.4 mo, respectively).

OS is an important secondary objective of RELAY. The sample size and study design were not intended to provide adequate power to detect statistically significant differences in OS. At the data cutoff, OS data were considered mature, with an overall event rate of 66% and an extended median follow-up time of 45.1 months (IQR: 26.7–71.2). RELAY reported no significant improvement in OS (HR = 0.98, 95% CI: 0.78–1.24, $p = 0.864$), with a directional improvement in mOS in favor of RAM + ERL (mOS = 51.1 mo) as compared with PBO + ERL (mOS = 46.0 mo). No significant improvements were observed in any of the preplanned subgroups either.

In general, the mOS, observed in RELAY was longer when compared with reported OS durations in other trials investigating EGFR-TKIs.[14] Whether or not the absence of CNS metastases is the only explanation for this finding remains open. The high number of Japanese patients and the high number of post-progression treatment lines might have had an impact on the survival results.

Table 1. Safety Overview and Discontinuation Due to Adverse Events in RAM + ERL and PBO + ERL Treatment Arms

Event (%)[a]	RAM + ERL (N = 221)	PBO + ERL (N = 225)
Any TEAE	100.0	100.0
Grade of ≥3 TEAEs	76.0	56.4
SAEs	32.6	22.7
Discontinued all study treatment due to TEAE	16.3	11.1
Discontinued all study treatment due to SAE	5.9	4.4
TEAEs leading to dose adjustment, any drug	86.9	72.0
TEAEs leading to death on study treatment[b]	1.4	0.0

[a]Patients may be counted in more than one category.
[b]Deaths are also included as serious adverse events and discontinuations due to adverse events.
PBO + ERL, Placebo + Erlotinib; RAM + ERL, ramucirumab + erlotinib; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

The OS outcome in the control arm is at the upper range of what has been reported for ERL monotherapy in contemporary randomized trials, with mOS between 23 and 51 months.[10,11,15–17] Like RELAY, these studies were not powered for OS, and OS outcomes did not reach statistical significance.

The overall favorable OS outcome across treatment arms may have increased the difficulty of observing an OS difference. Clinical trials with a PFS benefit and a long post-progression survival (PPS) have reduced statistical power to detect an improvement in OS,[18] as the types and frequencies of postprogression therapies can significantly impact OS outcomes. A statistical benefit in PFS might not translate into an OS benefit when the median PPS is large, like in RELAY. Post-progression therapies in RELAY were similar between treatment arms. More than 80% of patients received second-line treatment, 60% received third-line, and more than 40% received fourth- or later-lines of therapy. This may have contributed to the favorable OS outcomes and the long PPS in both treatment arms.

The most common mechanism of acquired resistance to first- and second-generation EGFR-TKIs is the development of T790M gatekeeper mutation.[12] In RELAY, the proportion of patients with T790M at progression was approximately 50% and similar between treatment arms. The proportion of patients receiving osimertinib was high (>50%) and similar between treatment arms. The median duration of osimertinib treatment regardless of line of therapy was longer than expected on the basis of AURA 3[19] and similar to real-world evidence data.[20]

Optimal treatment sequencing is crucial to maximize patient outcomes and prolong OS. The randomized phase 2 APPLE trial suggests that sequential treatment with gefitinib (a first-generation TKI) followed by osimertinib provides similar survival outcomes compared with upfront osimertinib.[21]

With the emergence of several promising treatment options for patients with *EGFR*-mutated NSCLC, the optimal strategy across multiple treatment lines remains unclear. Understanding resistance mechanisms and determining appropriate therapies on the basis of molecular resistance profiles remain important considerations. 1L treatment with the RELAY regimen offers the benefit of preserving both osimertinib and chemotherapy for later lines of therapy.

The overall OS effect from the addition of RAM to ERL seems mainly driven by the benefit in patients with L858R (HR = 0.87, 95% CI: 0.62–1.22), whereas patients with an exon 19del did not exhibit an OS benefit (HR = 1.13, 95% CI: 0.83–1.55), albeit with overlapping 95% CIs. A similar trend of longer OS in the RAM + ERL arm was observed in patients exhibiting a *TP53* co-mutation (HR = 0.83, 95% CI: 0.58–1.19) with no benefit in patients with wild-type *TP53* (HR = 1.22, 95% CI: 0.87–1.72). Consistent findings for the subgroups of *EGFR* mutation subtype and *TP53* co-mutation status were also observed for PFS.[22,23]

This extends to other reports that the addition of a VEGF inhibitor improves outcomes in these poor prognostic subsets[24–26] and is representative of a broader trend in which the impact of combination therapies may be more apparent in higher-risk populations

The ongoing REVOL858R phase 3 study evaluating the efficacy of RAM + ERL versus osimertinib in previously untreated patients with L858R mutant metastatic NSCLC is designed to prospectively explore the optimal treatment for these patients.[27] Insights into the molecular differences between exon 19del and L858R also guide future research, with the development of new inhibitors or combination strategies that specifically address the less responsive nature of L858R[28–30] to TKI monotherapy. These findings provide a rationale for treatment intensification for this subset of patients.

TP53 is implicated in angiogenesis and multiple studies have shown that the presence of a *TP53* co-mutation is associated with upregulation of the VEGF pathway.[31,32] This may provide a biological explanation for improved outcomes with dual EGFR/VEGF pathway inhibition in patients with a *TP53* co-mutation.[31,33,34] Treatment intensification strategies with VEGF inhibitors or other therapies, such as chemotherapy, are currently under active investigation or have reported favorable outcomes in the subset of patients with a *TP53* co-mutation.[23–26,35]

Overall safety was consistent with established profiles for RAM and ERL and as previously reported for RELAY,[9,36] with no increased toxicity over time and no new safety signals observed. Inconvenience owing to

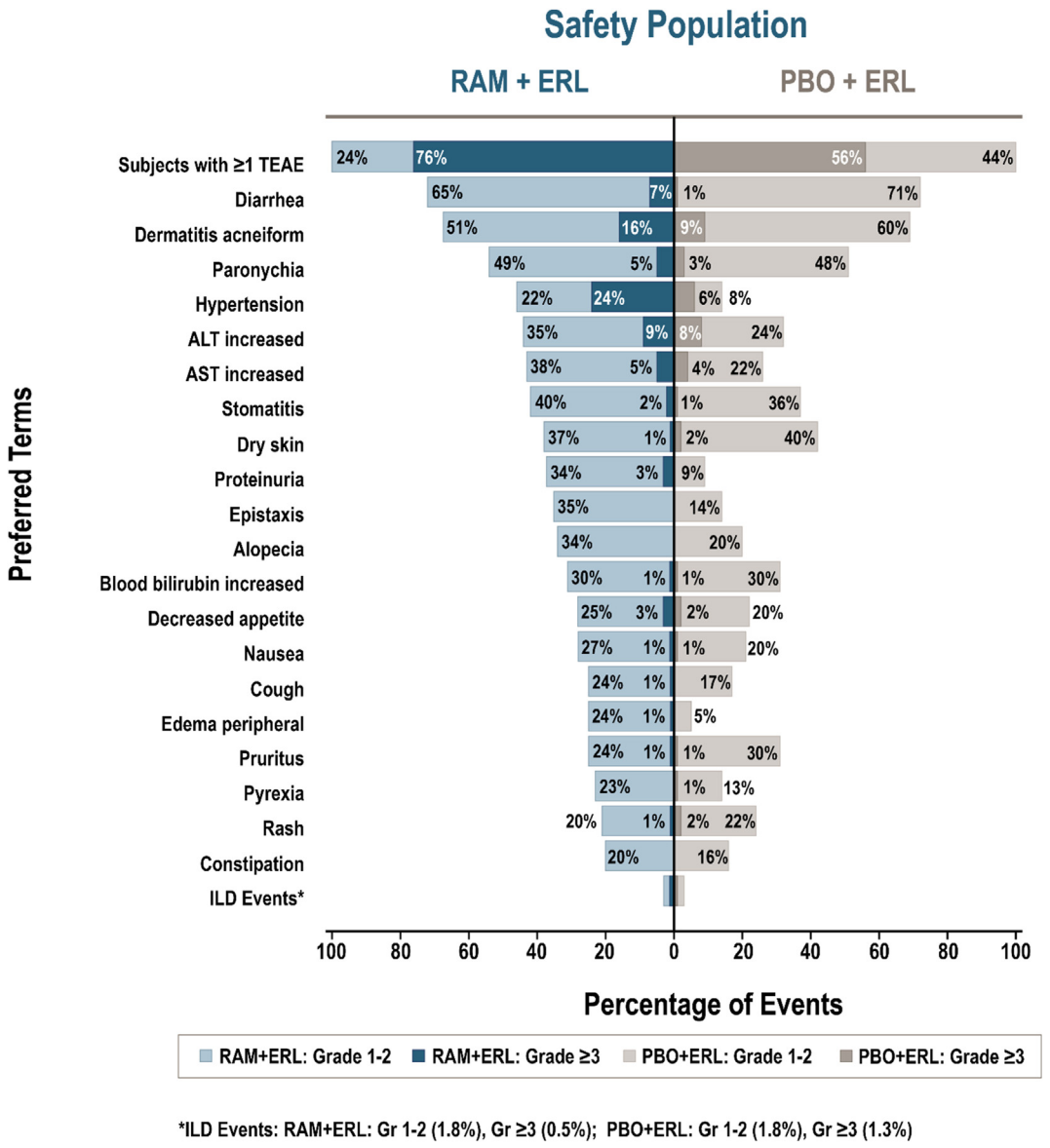


Figure 5. Tornado plot summarizing the TEAEs occurring in $\geq$ 20% of patients in the RAM + ERL arm. TEAE, treatment-emergent adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Gr, Grade; ILD, interstitial lung disease; PBO + ERL, placebo + erlotinib; RAM + ERL, ramucirumab + erlotinib; TEAE, treatment-emergent adverse events.

intravenous administration and the increased rate of toxicity remain concerns to combination treatment. Despite increased toxicity, quality of life results were not different between treatment arms.[37]

The RELAY trial faced several limitations. Notably, the study was not powered for OS. Although RAM and ERL have CNS activity,[38,39] RELAY did not include patients with CNS metastases, which might have enriched our population for patients with better prognoses. In addition, RELAY is not reflective of current treatment practices, as it does not account for the adoption of osimertinib as 1L treatment, which became the preferred standard of care after the trial's initiation in 2016.[40]

Since the initiation of RELAY, the treatment landscape for *EGFR*-mutated NSCLC has changed substantially. Studies exploring if the efficacy of third-generation EGFR-TKIs can be improved by the addition of chemotherapy, VEGF-inhibition, or MET-inhibition recently reported prolonged PFS in favor of the combination regimen (FLAURA2,[29,41] RAMOSE,[42] MARIPOSA[43]). Whether these treatment intensification strategies will ultimately provide a more prolonged OS as compared with a sequential treatment approach and if these should be offered to all or only select high-risk patients are important clinical questions that remain to be answered.

With the emergence of several promising treatment options for patients with metastatic *EGFR*-mutated NSCLC and the integration of osimertinib in the adjuvant and consolidation setting after curative-intent treatment, the challenge moving forward will be to integrate all these data into clinical practice, as the optimal strategy across multiple treatment lines is currently unclear. Understanding the potential impact of clinical and genomic patient and disease characteristics that lead to a poorer prognosis or reduced benefit of EGFR-TKI monotherapy may inform treatment decisions and help provide a personalized treatment strategy for patients with *EGFR* mutation.

CRediT Authorship Contribution Statement

Kazuhiko Nakagawa: Conceptualization, Methodology, Investigation, Writing - review & editing.

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Takashi Seto: Conceptualization, Methodology, Investigation, Writing - review & editing.

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Data Sharing Statement

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, except pharmacokinetic or genetic data. Data are available to request six months after the indication studied has been approved in the United States and European Union 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.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2024.11.032.

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