

# RELAY<sup>+</sup>: Exploratory Study of Ramucirumab Plus Gefitinib in Untreated Patients With EGFR-Mutated Metastatic NSCLC



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## ABSTRACT

**Introduction:** Ramucirumab (RAM) plus erlotinib was found to have superior progression-free survival (PFS) versus placebo plus erlotinib in untreated *EGFR*-mutated metastatic NSCLC in the global phase 3 RELAY study. RELAY+ was an open-label, two-period, single-arm, exploratory study of RAM plus gefitinib (GEF; period 1) and RAM plus osimertinib (period 2) in East Asia (NCT02411448).

**Methods:** Period 1 evaluated RAM (10 mg/kg) plus GEF (250 mg/d) in patients with untreated *EGFR*-mutated metastatic NSCLC. Period 2 evaluated RAM plus osimertinib (80 mg/d) in patients with disease progression who acquired T790M mutation in period 1. Exploratory end points included 1-year PFS rate (primary), other efficacy parameters, safety, and biomarker analyses of plasma (baseline, on-treatment, follow-up) using next-generation sequencing.

**Results:** From December 2017 to August 2018, a total of 82 patients were enrolled and started treatment (period 1, RAM + GEF). The 1-year PFS rate was 62.9% (95% confidence interval: 50.3–73.1). Treatment-emergent adverse events of grade three or higher were reported with RAM plus GEF in 60 of 82 patients (73.2%; five patients [6.1%] grade four). There were two deaths owing to adverse events that occurred (acute cardiac failure, congestive cardiac failure). T790M rate at disease progression in plasma was 81.0% (13 of 16 patients).

**Conclusions:** RELAY+ was found to have a favorable benefit–risk profile for RAM plus GEF in first-line treatment of East Asian patients with *EGFR*-mutated NSCLC.

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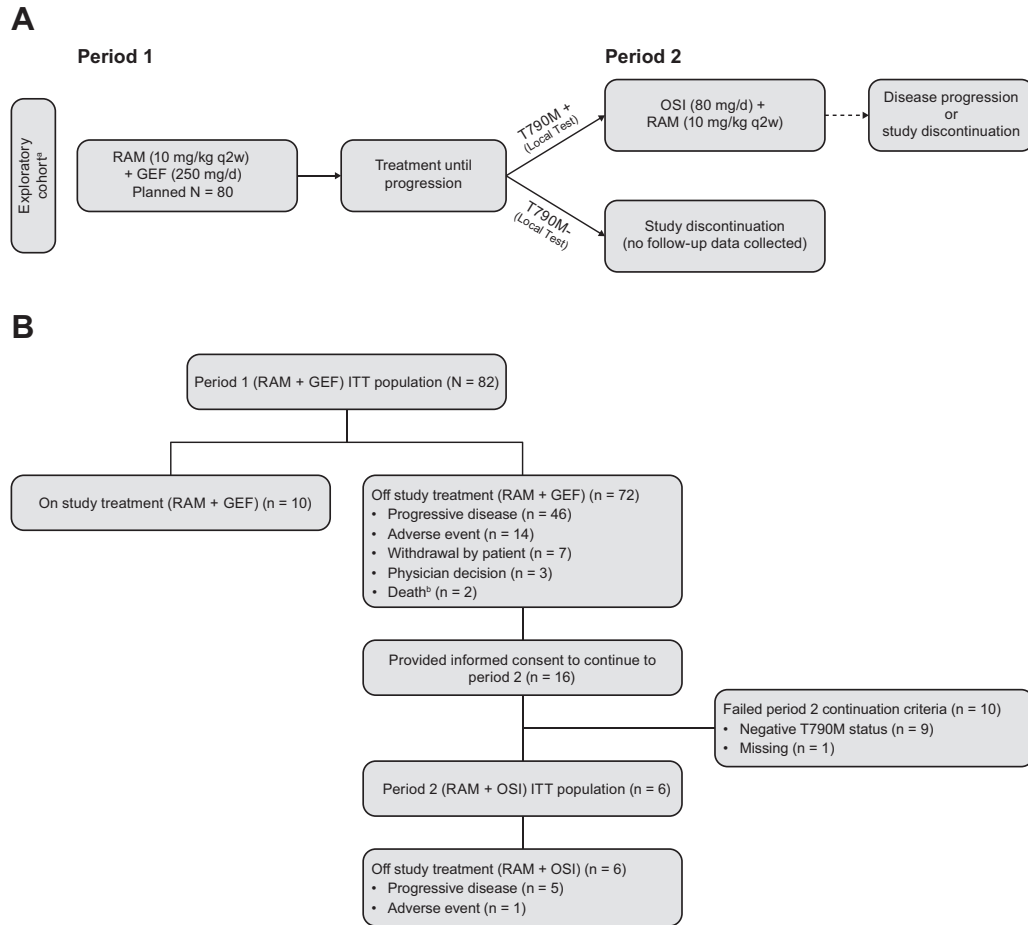
**Keywords:** East Asia; Japan; Plasma biopsy; Treatment outcome; Vascular endothelial growth factor receptor-2

## Introduction

In East Asia, lung cancer has the highest incidence and mortality rate of all cancers.<sup>1</sup> Approximately 50% of tumors from Asian patients with adenocarcinoma NSCLC have an *EGFR* gene mutation.<sup>2</sup> The prevalence of *EGFR* mutations is higher in Asian populations than in white populations (approximately 40% versus 20%).<sup>3</sup> In-frame deletions of exon 19 (ex19del) and an L858R point mutation in exon 21 (ex21.L858R) are the most common types of activating *EGFR* mutations, accounting for up to 46% and 39%, respectively, of mutations in the tyrosine kinase domain of the *EGFR* gene in *EGFR*-mutated NSCLC.<sup>4,5</sup>

*EGFR* tyrosine kinase inhibitors (TKIs) are standard-of-care first-line treatment for *EGFR*-mutated NSCLC.<sup>6–8</sup> Nevertheless, many patients eventually develop treatment resistance and experience disease progression on *EGFR* TKI therapy. Approximately 30% to 60% of patients with NSCLC treated with first- and second-generation *EGFR* TKIs acquire the *EGFR* T790M resistance mutation, whereas resistance mechanisms to the third-generation *EGFR* TKI osimertinib (OSI) are heterogeneous and mostly not targetable.<sup>9,10</sup> After targeted treatments are exhausted, chemotherapy is the recommended treatment option.<sup>8,11,12</sup> Additional treatment options to enhance the long-term efficacy of *EGFR* TKIs are therefore required.

Dual inhibition of the *EGFR* and vascular endothelial growth factor (VEGF) pathways has been found to be a viable treatment strategy to improve outcomes for patients with *EGFR*-mutated NSCLC.<sup>13,14</sup> Using this strategy, promising efficacy has been shown in several clinical studies (JO25567, NEJ026, CTONG 1509, and RELAY), all of which have combined erlotinib (ERL), an *EGFR* TKI, with a VEGF inhibitor.<sup>14–17</sup> RELAY was a global, phase 3, double-blind, randomized, placebo-controlled study investigating the efficacy and safety of the addition of ramucirumab (RAM), a human IgG1 VEGF receptor 2 antagonist, to ERL (RAM + ERL) in treatment-naïve *EGFR*-mutated metastatic NSCLC.<sup>17</sup> Progression-



**Figure 1.** RELAY+ exploratory open-label cohort: (A) study design and (B) patient disposition. <sup>a</sup>The exploratory cohort included patients enrolled in Japan, South Korea, and Taiwan. <sup>b</sup>Death due to adverse event. One patient died due to acute cardiac failure and one patient died due to congestive cardiac failure. Both events were considered related to the study treatment. Data cutoff date: November 25, 2020. GEF, gefitinib; ITT, intent-to-treat; OSI, osimertinib; q2w, once every 2 weeks; RAM, ramucirumab.

free survival (PFS) was superior with RAM plus ERL treatment compared with placebo (PL) plus ERL (PL + ERL) (median PFS = 19.4 mo versus 12.4 mo; hazard ratio [HR] = 0.59 [95% confidence interval (CI): 0.46–0.76],  $p < 0.0001$ ; 1-y PFS rate: 71.9% [95% CI: 65.1–77.6] versus 50.7% [95% CI: 43.7–57.3] for RAM + ERL and PL + ERL, respectively).<sup>17</sup> The PFS benefit was consistent for ex19del and ex21.L858R subgroups. The safety profile in RELAY was consistent with established safety profiles of RAM and ERL in metastatic *EGFR*-mutated NSCLC.<sup>17</sup> Similar efficacy and safety results were observed in the Japanese and East Asian RELAY subset populations.<sup>18,19</sup> *EGFR* T790M mutation rates after disease progression evaluated by next-generation sequencing (NGS) of plasma samples indicated that the addition of RAM to ERL did not affect the T790M rate but might delay the emergence of T790M.<sup>17–19</sup>

ERL and gefitinib (GEF) are first-generation *EGFR* TKIs used for first-line treatment of *EGFR*-mutated NSCLC. *EGFR* variants have been found in preclinical studies to have different sensitivity to ERL and GEF,<sup>20</sup> and in the clinical setting ERL is used at its maximum tolerated dose, whereas GEF is used at submaximum tolerated dose levels.<sup>21–23</sup> RELAY+, an additional cohort of RELAY, was an open-label, two-period, single-arm, exploratory study designed to evaluate the efficacy and safety of RAM plus GEF (RAM + GEF; period 1) for the first-line treatment of East Asian (Japanese, South Korean, Taiwanese) patients with metastatic *EGFR*-mutated NSCLC. In addition, the safety of RAM plus OSI (RAM + OSI; period 2) was evaluated in patients who had progressed on RAM plus GEF and acquired the T790M mutation during period 1. We report efficacy and safety results for period 1 and safety results for period 2.

## Materials and Methods

### Study Design

RELAY+ (part C addendum of the RELAY study<sup>17</sup>; [www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT02411448) was an open-label, two-period, single-arm, exploratory study conducted in Japan, South Korea, and Taiwan (Fig. 1A). Period 1 evaluated the efficacy and safety of RAM plus GEF in patients with untreated *EGFR*-mutated metastatic NSCLC. Period 2 evaluated the safety of RAM plus OSI in patients who had progressed on RAM plus GEF in period 1 and had developed the T790M mutation. Two exploratory biomarker studies were conducted; the first in the intent-to-treat populations and the second an optional exploratory liquid biopsy addendum specific to patients enrolled in Japan. Ethics review boards of each site approved the study protocol and addendum. The study was conducted in accordance with the Declaration of Helsinki, The Council for International Organizations of Medical Sciences International Ethical Guidelines, Good Clinical Practice guidelines, and local guidelines. All patients provided written informed consent.

### Study Population

Patient inclusion and exclusion criteria were the same as those for RELAY.<sup>17</sup> Briefly, patients were 18 years of age and older ( $\geq 20$  y in Japan and Taiwan), previously had untreated stage IV NSCLC (defined by the American Joint Committee on Cancer Staging criteria for lung cancer), an Eastern Cooperative Oncology Group performance status of 0 or 1, no central nervous system metastases, and documented evidence by local testing methods (therascreen, cobas, etc.) that the tumor was positive for *EGFR* ex19del or ex21.L858R mutation. Patients known to have the T790M mutation were excluded.

### Treatment Protocol

In period 1, the patients received RAM (10 mg/kg administered intravenously every 2 wk) plus GEF (250 mg orally once daily). In period 2, the eligible patients received RAM (10 mg/kg every 2 wk) plus OSI (80 mg orally once daily). Patients were eligible for period 2 if they had disease progression in period 1 and had confirmed T790M-positive metastatic NSCLC (Fig. 1A; [Supplementary Methods](#)). Patients received treatment (RAM + GEF; RAM + OSI) until disease progression according to Response Evaluation Criteria in Solid Tumours version 1.1, unacceptable toxicity to either drug, noncompliance, or investigator or patient decision.

### Outcome Measures

Primary end point was 1-year PFS rate (investigator-assessed) in period 1. Secondary end points included the

following: overall survival (OS) rates; objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and second occurrence of progressive disease (PFS2). Outcome measures are defined in the [Supplementary Methods](#). The safety of RAM was assessed by the occurrence of adverse events (AEs) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

### Biomarker Analyses

Liquid biopsy samples at baseline and at postperiod 1 study treatment discontinuation (30-d follow-up) were analyzed by Guardant360 (Guardant Health, Redwood City, CA) NGS<sup>17</sup> for T790M and *TP53* mutations. Plasma samples from patients enrolled in the exploratory liquid biopsy addendum were collected at baseline, during treatment (cycle 4, cycle 13, and every six cycles until progression), and at 30-day follow-up for circulating tumor DNA (ctDNA) assessment. Somatic mutations and copy number variation were analyzed by droplet digital polymerase chain reaction (ddPCR).

### Statistical Analysis

Approximately 80 patients with untreated *EGFR*-mutated metastatic NSCLC were planned to be enrolled and treated with RAM plus GEF ([Supplementary Methods](#)). Data cutoff dates were November 25, 2020 (efficacy, safety, and Guardant360 results), and February 8, 2021 (exploratory liquid biopsy addendum results).

Efficacy end points were evaluated in the period 1 intent-to-treat population (all patients enrolled to RAM + GEF in period 1); efficacy data were investigator-assessed. PFS, PFS2, OS, and DOR rates were estimated using the Kaplan-Meier method; corresponding 95% CIs were estimated using Brookmeyer and Crowley, or Greenwood, methods. Patients were censored at the date of their last radiographic tumor assessment if, at the data cutoff date, it was not known if they had died or had disease progression. ORR and DCR were calculated as defined by Response Evaluation Criteria in Solid Tumours version 1.1; 95% CIs were calculated using the Clopper-Pearson method. Patients with no postbaseline tumor response assessments for any reason were considered nonresponders and were included in the denominator when calculating the response rate. DOR analysis was for responders only; if a responder was not known to have died or have objective progression, then the patient was censored at the date of last evaluable tumor assessment.

Safety end points were assessed in the safety analysis populations (period 1 safety population, all patients who received at least one dose of any study treatment in



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

Characteristics <sup>a</sup>	RAM + GEF (N = 82)
<b>Sex</b>	
Female	54 (65.9)
Male	28 (34.1)
<b>Age, y</b>	
Median	68
Min-max	44-85
<b>Race</b>	
Asian	82 (100)
<b>Country</b>	
Japan	68 (82.9)
South Korea	6 (7.3)
Taiwan	8 (9.8)
<b>Smoking history</b>	
Ever	26 (31.7)
Never	54 (65.9)
Unknown or missing	2 (2.4)
<b>ECOG PS</b>	
0	43 (52.4)
1	39 (47.6)
<b>Disease classification</b>	
Primary metastatic	61 (74.4)
Recurrent metastatic	21 (25.6)
<b>EGFR mutation type</b>	
Exon 19 deletion	36 (43.9)
Exon 21 (L858R) mutation	46 (56.1)
<b>EGFR testing method<sup>b</sup></b>	
therascreen and cobas	32 (39.0)
Other PCR and sequencing-based methods	50 (61.0)

<sup>a</sup>Except where otherwise indicated, data are n (%).

<sup>b</sup>Determined by local testing.

ECOG PS, Eastern Cooperative Oncology Group performance status; GEF, gefitinib; ITT, intent-to-treat; max, maximum; min, minimum; PCR, polymerase chain reaction; RAM, ramucirumab.

period 1; period 2 safety population, all patients who received at least one dose of any study treatment in period 2) and summarized by each period. AEs, treatment-emergent AEs (TEAEs), AEs of special interest, and serious AEs were summarized as counts and percentages of patients reporting each event.

Guardant360 T790M analysis populations comprised patients with 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). Patients with at least one alteration detected in their baseline NGS sample were included in an additional analysis population for potential prognostic effect of TP53 mutations. T790M mutation rates and associated Wilson score 95% CIs were determined. For the exploratory liquid biopsy addendum, the translational research ddPCR (TR-ddPCR) population comprised patients with a valid baseline sample (passed quality control for ddPCR). PFS was

estimated using the Kaplan-Meier method; HRs and corresponding 95% CIs were estimated using Cox regression models. Prognostic effects of baseline patient characteristics (EGFR mutation detected by ddPCR [detected versus not detected], sex [male versus female], disease stage [metastatic disease versus recurrent metastatic disease], Eastern Cooperative Oncology Group performance status [1 versus 0], smoking history [other versus never], and age [≥65 versus <65 y]) on PFS were estimated using univariable and multivariable Cox proportional hazards regression and illustrated graphically using forest plots.

## Results

### Patient Disposition and Baseline Demographics

RELAY+ study enrollment occurred on December 18, 2017, to August 16, 2018. A total of 82 patients were enrolled and treated in period 1 (Fig. 1B). At data cutoff, 10 patients (12.2%) in period 1 remained on the study treatment and 72 patients (87.8%) had discontinued period 1 study treatment (Fig. 1B). The most common reasons for period 1 study treatment discontinuation were progressive disease (56.1%; 46 of 82 patients) and AEs (17.1%; 14 of 82 patients). Of the patients who had disease progression on RAM plus GEF in period 1, 16 patients provided informed consent to continue into period 2; six patients (37.5%) met the criteria to continue into period 2. The main reason for not meeting the criteria was negative T790M status on the basis of local testing (Fig. 1B). At data cutoff, all patients in period 2 (RAM + OSI) had discontinued study treatment (Figs. 1B and 2). The reasons for period 2 study treatment discontinuation were progressive disease (83.3%; five of six patients) and an AE (16.7%; one of six patients).

Baseline characteristics reflected the East Asian patient population with metastatic NSCLC with EGFR-activating mutations,<sup>2,24</sup> excluding patients with central nervous system metastasis (Table 1). Most patients in period 1 were Japanese (82.9%), female (65.9%), had never smoked (65.9%), and had a diagnosis of primary metastatic disease (74.4%); median age was 68 years. The most common EGFR-activating mutation was ex21.L858R (56.1%) compared with ex19del mutation (43.9%). Of the six patients who continued into period 2, median age (minimum [min]–maximum [max]) was 63.5 (56–80) years, three patients (50.0%) were female, and four (66.7%) had an ex19del mutation (Supplementary Table 1).

### Efficacy

At data cutoff, median follow-up time was 27.6 (min–max: 2.6–35.3) months. The 1-year PFS rate with

**Table 2. Efficacy End Points (Period 1 ITT Population)**

Variables	RAM + GEF (N = 82)
<b>PFS</b>	
Events, n (%)	54 (65.9)
Patients censored, n (%)	28 (34.1)
Median (95% CI), mo	14.1 (12.3-17.9)
PFS rate, % (95% CI)	
12 mo (1 y)	62.9 (50.3-73.1)
18 mo	38.3 (26.8-49.8)
24 mo (2 y)	26.1 (16.2-37.0)
30 mo	17.2 (8.6-28.4)
Best overall response, n (%)	
CR	1 (1.2)
PR	57 (69.5)
Stable disease	23 (28.0)
PD	1 (1.2)
NA	1 (1.2)
ORR (CR/PR), n	
% (95% CI)	58 70.7 (59.7-80.3)
DCR (CR/PR/stable disease), n	
% (95% CI)	81 98.8 (93.4-100.0)
<b>DOR<sup>a</sup></b>	
Events, n (%)	42 (72.4)
Patients censored, n (%)	16 (27.6)
Median (95% CI), mo	14.0 (11.1-16.7)
DOR survival rate, % (95% CI)	
6 mo	80.1 (67.0-88.5)
12 mo (1 y)	60.7 (46.3-72.4)
18 mo	31.3 (19.3-44.1)
<b>OS</b>	
Events, n (%)	22 (26.8)
Patients censored, n (%)	60 (73.2)
Median (95% CI), mo	NA
OS rate, % (95% CI)	
12 mo (1 y)	94.9 (87.0-98.1)
18 mo	85.8 (75.9-91.9)
24 mo (2 y)	79.3 (68.5-86.8)
30 mo	69.3 (55.8-79.4)
<b>PFS2<sup>b</sup></b>	
Events, n (%)	37 (45.1)
Patients censored, n (%)	45 (54.9)
Median (95% CI), mo	NA
PFS2 rate, % (95% CI)	
12 mo (1 y)	86.0 (76.2-92.0)
18 mo	78.2 (67.3-85.8)
24 mo (2 y)	58.6 (46.9-68.7)
30 mo	50.5 (38.3-61.5)

<sup>a</sup>In patients who responded (n = 58).

<sup>b</sup>Time from enrollment 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; CR, complete response; DCR, disease control rate; DOR, duration of response; GEF, gefitinib; ITT, intent-to-treat; NA, not assessable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, second occurrence of progressive disease; PR, partial response; RAM, ramucirumab.

RAM plus GEF was 62.9% (95% CI: 50.3–73.1); 2-year PFS rate was 26.1% (95% CI: 16.2–37.0) (Table 2). Median PFS was 14.1 months (95% CI: 12.3–17.9) (Fig. 3). Subgroup analyses for *EGFR* mutation type

were performed; 1-year PFS rate (95% CI) was 67.2% (48.6–80.3) and 59.2% (41.4–73.3) for ex19del and ex21.L858R subgroups, respectively. Overall ORR was 70.7% (95% CI: 59.7–80.3), and DCR was 98.8% (95% CI: 93.4–100.0) (Table 2). For patients who responded to RAM plus GEF treatment (42 of 58 patients; 72.4%), median DOR was 14.0 months (95% CI: 11.1–16.7). DOR rates (95% CI) at 6, 12, and 18 months were 80.1% (67.0–88.5), 60.7% (46.3–72.4), and 31.3% (19.3–44.1), respectively. OS and PFS2 were immature (censoring rates, 73.2% and 54.9%, respectively). The OS rate (95% CI) was 94.9% (87.0–98.1) and 79.3% (68.5–86.8) at 1 and 2 years, respectively. The PFS2 rate was 86.0% (76.2–92.0) and 58.6% (46.9–68.7) at 1 and 2 years, respectively (Table 2).

### Treatment Exposure

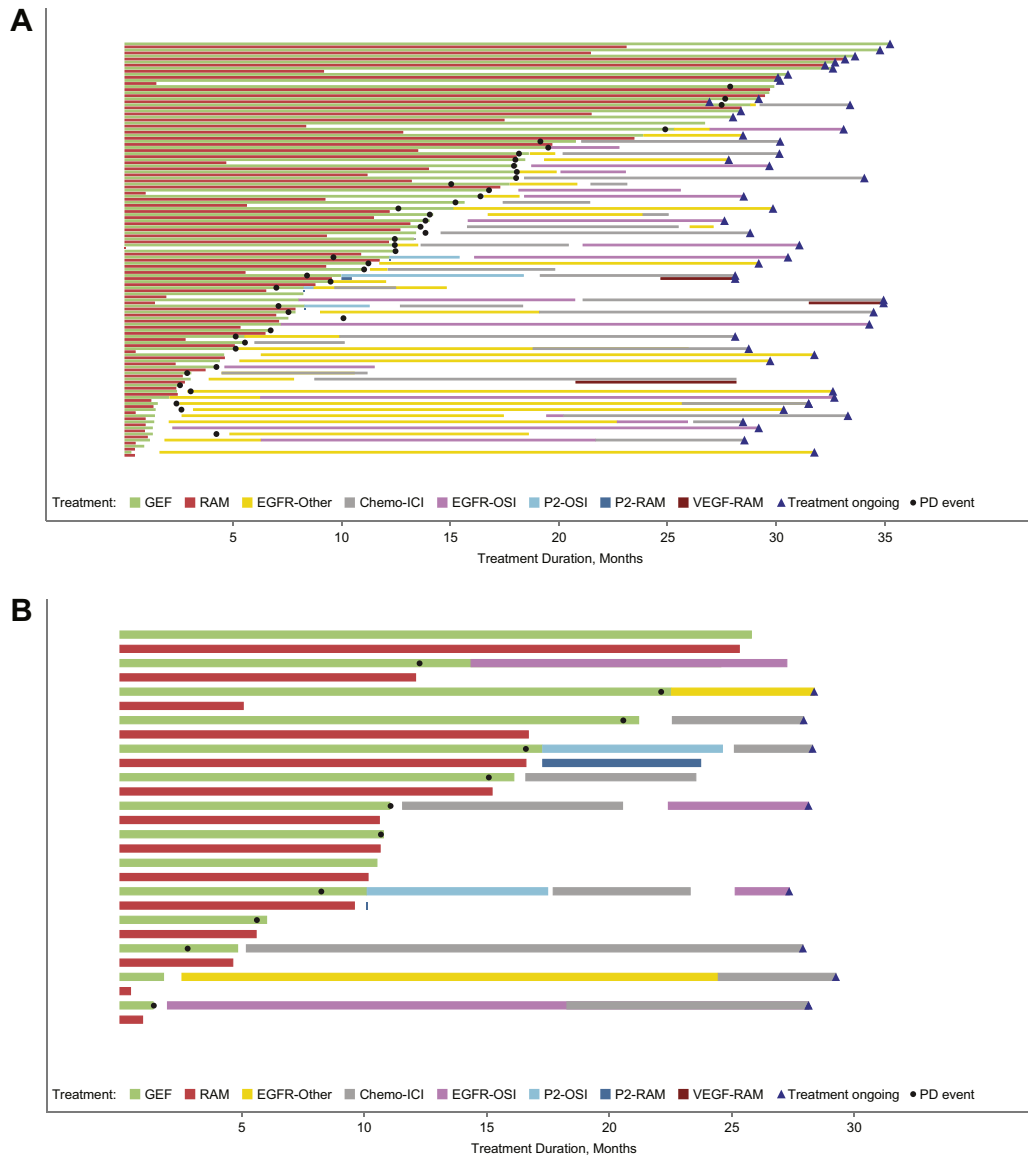
In period 1 (safety population, N = 82), median (min–max) duration of exposure was 8.7 (0.5–33.6) and 11.8 (0.3–35.3) months, and median relative dose intensity was 95.0% and 99.6%, for RAM and GEF, respectively. In period 2 (safety population, n = 6), patients received RAM for a range of 15 to 225 days, with four patients discontinuing RAM within 42 to 54 days owing to an AE (grade 1 or 2) of decreased platelet count. Patients received OSI for a range of 15 to 270 days, with five patients discontinuing owing to progressive disease and one patient owing to an AE (grade 1) of decreased left ventricular ejection fraction. The median relative dose intensity was 100.0% and 98.7% for RAM and OSI, respectively.

### Postperiod 1 Therapy

Of the 72 patients who had discontinued period 1 study treatment, 59 patients received subsequent systemic therapy, including chemotherapy (n = 34), EGFR TKI therapy (n = 50), immunotherapy (n = 10), VEGF antibody therapy (n = 17), or unknown treatment type (n = 2) (Supplementary Table 2). Overall, 25 of 72 patients (34.7%) who had discontinued period 1 study treatment received OSI as a subsequent treatment, six of whom received OSI as period 2 study treatment. OSI was received as a first, second, third, and fourth subsequent line of treatment by 16, seven, three, and one patients, respectively, with three patients in Japan receiving the maximum of five subsequent lines of postperiod 1 treatment (Supplementary Table 2). Japanese patients tended to continue GEF after discontinuing RAM in period 1 and received EGFR TKI therapy (other than OSI) after period 1 more frequently than non-Japanese patients (Fig. 2).

### Safety

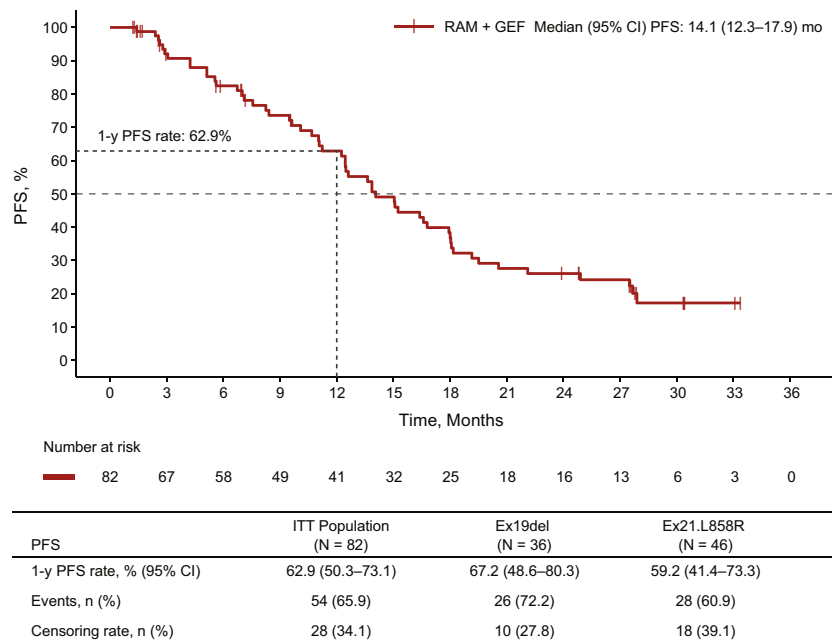
All patients in the period 1 safety population (RAM + GEF; N = 82) reported at least one TEAE



**Figure 2.** Swimmer plot of treatment sequence for (A) Japanese patients and (B) non-Japanese patients (RELAY+ period 1 ITT population). EGFR-Other = gefitinib, erlotinib, or afatinib as postdiscontinuation treatment; Chemo-ICI = chemotherapy/immunotherapy/PD-(L)1 inhibitor; EGFR-OSI = osimertinib; P2-OSI = osimertinib received in period 2; P2-RAM = ramucirumab received in period 2; VEGF-RAM = ramucirumab as postdiscontinuation treatment. Chemo, chemotherapy; GEF, gefitinib; ICI, immune checkpoint inhibitor; ITT, intent-to-treat; OSI, osimertinib; P2, period 2; PD, progressive disease; PD-(L)1, programmed death-(ligand) 1; RAM, ramucirumab; VEGF, vascular endothelial growth factor.

(Table 3). Any-grade TEAEs occurring in 50% of patients or more with RAM plus GEF treatment included dermatitis acneiform (69.5%), increased level of aspartate aminotransferase (AST; 63.4%), diarrhea (62.2%), increased level of alanine aminotransferase (ALT; 61.0%), and hypertension (51.2%). TEAEs of grade three or higher were reported by 60 of 82 patients (73.2%). TEAEs of grade three or higher occurring at a frequency of more than 15% were hypertension (25.6%, all grade 3) and increased ALT level (23.2%, all grade 3) (Table 3). Overall, five patients (6.1%) had grade four TEAEs, which were aortic valve stenosis, ileus, increased AST

level, pneumonitis, and laryngeal obstruction (one patient each, 1.2%). Any-grade AEs of special interest for antiangiogenic agents included bleeding or hemorrhage, 52.4% (primarily driven by low-grade epistaxis; grade  $\geq 3$  bleeding, 1.2%); hypertension, 51.2% (grade  $\geq 3$ , 25.6%); proteinuria, 48.8% (grade  $\geq 3$ , 2.4%); liver injury or liver failure, 75.6% (grade  $\geq 3$ , 26.8%); and infusion-related reactions, 1.2% (grade 2) (Table 3). In total, 26 patients (31.7%) in the period 1 safety population had at least one serious AE. Two patients died due to AEs on study treatment (RAM + GEF); events included acute cardiac failure and congestive cardiac failure (one



**Figure 3.** Kaplan-Meier plot of investigator-assessed 1-year PFS rate (period 1 ITT population). CI, confidence interval; ex19del, in-frame deletions of exon 19; ex21.L858R, L858R point mutation in exon 21; GEF, gefitinib; ITT, intent-to-treat; PFS, progression-free survival; RAM, ramucirumab.

patient each; 1.2%). Both events were deemed by the investigator as related to the study treatment.

All patients in the period 2 safety population (RAM + OSI; n = 6) reported at least one TEAE (Supplementary Table 3). Grade three TEAEs were reported by three of six patients (50.0%) and included diarrhea, decreased neutrophil count, decreased white blood cell count, pleural effusion, dermatitis acneiform, and pleurodesis (one patient each); no grade four events were observed. One patient discontinued study treatment owing to an AE (grade one ejection fraction decreased); no patient in the period 2 safety population died owing to an AE.

### Biomarker Analyses

**Guardant360 Central Assessment.** The baseline *TP53* mutation rate was 41.7% (30 of 72 evaluable patients); 58.3% (42 of 72 evaluable patients) were wild-type for *TP53*. Median PFS by baseline *TP53* status was 10.7 versus 18.1 months (HR = 0.38 [95% CI: 0.22–0.68]) in the *TP53* mutated versus *TP53* wild-type groups, respectively (Supplementary Fig. 1). Treatment-emergent postprogression T790M rates were 48.0% (12 of 25 patients; 95% CI: 30.0–66.5) for population 1 and 81.0% (13 of 16 patients; 95% CI: 57.0–93.4) for population 2 (i.e., NGS results at 30-d follow-up contained an *EGFR*-activating mutation).

**Exploratory Liquid Biopsy Addendum.** Of the 68 patients enrolled in Japan, 48 patients participated in the

optional exploratory liquid biopsy addendum. The TR-ddPCR population comprised 46 patients with valid baseline assay results (Supplementary Fig. 2). Median PFS was shorter for patients with an *EGFR*-activating mutation detected in ctDNA (n = 24) at baseline by ddPCR compared with patients with no *EGFR*-activating mutation detected in ctDNA (n = 22) at baseline (12.5 versus 27.7 mo, respectively; HR = 0.24 [95% CI: 0.10–0.57]) (Supplementary Fig. 3A). In the TR-ddPCR population, *EGFR*-activating mutation allele frequency decreased from cycle 4 and remained suppressed throughout treatment (Supplementary Fig. 3B). Median PFS was not different between patients with an *EGFR*-activating mutation detected at cycle 4 (n = 6) and patients with no *EGFR*-activating mutation detected at cycle 4 (n = 40) (Supplementary Fig. 4). Primary metastatic disease at baseline was identified as a negative prognostic factor by univariable analysis (HR = 0.20 [95% CI: 0.05–0.83]), but this was not confirmed by multivariable analyses. A detectable *EGFR*-activating mutation (ddPCR) in ctDNA was identified as a negative prognostic factor for PFS duration by both univariable (HR = 0.24 [95% CI: 0.10–0.57], Supplementary Fig. 3C) and multivariable regression analyses (HR = 0.26 [95% CI: 0.09–0.75]; Supplementary Fig. 3D).

### Discussion

This is the first exploratory study to investigate RAM plus GEF treatment in East Asian patients with untreated



**Table 3.** TEAEs Occurring in ≥30% of Patients and AESIs for RAM (Period 1 Safety Population)

Event	RAM + GEF (N = 82)	
	Any grade	Grade ≥3
TEAEs, n (%)		
≥1 TEAE	82 (100.0)	60 (73.2)
Dermatitis acneiform	57 (69.5)	3 (3.7)
Increased AST	52 (63.4)	10 (12.2)
Diarrhea	51 (62.2)	5 (6.1)
Increased ALT	50 (61.0)	19 (23.2)
Hypertension	42 (51.2)	21 (25.6)
Proteinuria	38 (46.3)	1 (1.2)
Paronychia	37 (45.1)	0 (0)
Stomatitis	37 (45.1)	0 (0)
Dry skin	29 (35.4)	0 (0)
Epistaxis	25 (30.5)	0 (0)
AESIs, n (%)	Any grade	Grade ≥3
Bleeding or hemorrhage	43 (52.4)	1 (1.2)
Epistaxis	25 (30.5)	0 (0)
GI hemorrhage	7 (8.5)	0 (0)
Pulmonary hemorrhage	2 (2.4)	0 (0)
Hypertension	42 (51.2)	21 (25.6)
Proteinuria	40 (48.8)	2 (2.4)
Liver injury or liver failure <sup>a</sup>	62 (75.6)	22 (26.8) <sup>b</sup>
Increased AST	52 (63.4)	10 (12.2)
Increased ALT	50 (61.0)	19 (23.2)
Increased blood bilirubin	12 (14.6)	0 (0)
Infusion-related reactions <sup>c</sup>	1 (1.2)	0 (0)
Other TEAE of interest, n (%)	Any grade	Grade ≥3
ILD <sup>d</sup>	2 (2.4)	2 (2.4) <sup>e</sup>

<sup>a</sup>Included events of increased GGT, abnormal hepatic function, and increased liver function tests.

<sup>b</sup>One patient had a grade four TEAE of increased AST level.

<sup>c</sup>Events that occurred on the day of RAM administration.

<sup>d</sup>ILD events were pneumonitis.

<sup>e</sup>One patient had a grade 4 TEAE of pneumonitis.

AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GEF, gefitinib; GGT, gamma-glutamyl transferase; GI, gastrointestinal; ILD, interstitial lung disease; RAM, ramucirumab; TEAE, treatment-emergent adverse event.

metastatic NSCLC with an *EGFR*-activating mutation. The 1-year PFS rate with RAM plus GEF was 62.9% (95% CI: 50.3–73.1). RAM plus GEF was well tolerated, no new safety concerns were identified, and the overall safety profile was consistent with the established safety profiles for RAM and GEF in *EGFR*-mutated metastatic NSCLC. The T790M rate at disease progression was 48.0% for patients with an NGS result at baseline and at 30-day follow-up and 81.0% for patients with an NGS result at 30-day follow-up containing an *EGFR*-activating mutation. More than one-third of patients (25 of 72) who discontinued RAM plus GEF treatment received OSI (six of whom received RAM + OSI) as a subsequent treatment during their full course of treatment post-disease progression. The totality of the efficacy and safety results reported for RAM plus GEF in patients with metastatic NSCLC with an *EGFR*-activating mutation

indicates that RAM plus GEF provides an alternative treatment option for patients with *EGFR*-mutated NSCLC.

GEF and ERL are widely used as monotherapy in East Asia for first-line treatment of patients with *EGFR*-mutated NSCLC.<sup>25,26</sup> Clinical studies with GEF and ERL monotherapy have revealed median PFS values of 9.2 to 10.8 months<sup>27–29</sup> and 9.7 to 13.1 months,<sup>30–32</sup> respectively. In the international Lux-Lung 7 study in patients with *EGFR*-mutated NSCLC (with and without brain metastases), median PFS and the 1-year PFS rate for GEF monotherapy were 10.9 months (95% CI: 9.1–11.5) and 41.3% (95% CI: 33.0–49.5), respectively.<sup>33</sup> Improvements in PFS were observed when GEF was combined with the VEGF inhibitor bevacizumab in a single-arm phase 2 study of Japanese patients with *EGFR*-mutated NSCLC (median PFS = 14.4 mo [95% CI: 10.1–19.2]; 1-y PFS rate: 56.7% [95% CI: 39.9–70.5])<sup>34</sup> and in RELAY+ with RAM plus GEF treatment (median PFS = 14.1 [95% CI: 12.3–17.9]; 1-y PFS rate = 62.9% [95% CI: 50.3–73.1]). In the phase 3 RELAY study, RAM plus ERL was compared with PL plus ERL and revealed improved efficacy with combination treatment (median PFS = 19.4 versus 12.4 mo, respectively; 1-y PFS rates = 71.9% versus 50.7%, respectively).<sup>17</sup> These studies provide further support that combination treatment such as RAM plus GEF or RAM plus ERL may be more beneficial than first-generation *EGFR* TKI monotherapy for the treatment of *EGFR*-mutated NSCLC.

Despite the pitfalls of indirect comparison of study outcomes, when compared with other studies, the RELAY+ results indicate that OS rates, although immature in this report, may be improved with RAM plus GEF compared with GEF monotherapy. In the Asian subset of FLAURA, a phase 3 double-blind study comparing OSI with GEF or ERL,<sup>35</sup> the 18-month OS rate for OSI versus GEF was 82% versus 72%, respectively,<sup>36</sup> both of which were numerically lower than the 18-month OS rate of 85.8% observed with RAM plus GEF in RELAY+. In ARCHER 1050,<sup>29</sup> a randomized, open-label, phase 3 study of dacomitinib versus GEF, OS rates at 30 months (median duration of follow-up was 31.3 mo) were 56.2% versus 46.3%, respectively.<sup>37</sup> In RELAY+, the 30-month OS rate (median follow-up duration, 27.6 mo) with RAM plus GEF treatment was 69.3%. Furthermore, the 18-month OS rates of RAM plus GEF observed in RELAY+ were comparable with those observed with RAM plus ERL in the East Asian subgroup population of RELAY (85.8% versus 87.2%, respectively).<sup>19</sup> Importantly, however, the FLAURA study included patients with brain metastases, but ARCHER 1050, RELAY+, and RELAY excluded these patients, and thus, this difference in the patient cohorts should be considered when comparing the OS rates of these studies.

Dermatitis acneiform, known to be associated with EGFR TKI treatment,<sup>38</sup> was reported in 69.5% of RELAY+ patients treated with RAM plus GEF; this was lower than the incidence reported in the RELAY East Asian subset population treated with RAM plus ERL (78.7%).<sup>19</sup> Paronychia, another skin toxicity associated with EGFR TKI treatment,<sup>39</sup> was reported at a lower incidence in RELAY+ (45.1%) than in RELAY with RAM plus ERL (East Asian subset, 61.0%).<sup>19</sup> Hypertension is a well-known class-related effect of VEGF/VEGF receptor antagonists.<sup>40</sup> In RELAY+, grade three hypertension was the most frequently reported (25.6%) grade three event, which was also observed in RELAY for both the East Asian and Japanese subset populations with RAM plus ERL.<sup>18,19</sup> AEs of special interest for RAM generally occurred at a higher incidence in RELAY+ (RAM + GEF) than in the RELAY East Asian safety population (RAM + ERL): hypertension (51.2% versus 42.7%), liver injury or liver failure (75.6% versus 66.5%), and proteinuria (48.8% versus 38.4%); an exception was bleeding and hemorrhage (52.4% versus 55.5%).<sup>19</sup> No new safety issues or concerns were identified, although liver injury events of grade three or higher were more common in RELAY+ than in RELAY, consistent with the established safety profile of GEF.<sup>41</sup> In period 2 (n = 6), low-grade decreased platelet count with no clinical sequelae was reported by four patients. Although the patient cohort was limited in size, RAM plus OSI treatment did not reveal any unexpected safety issues.

Japanese patients are at higher risk of developing interstitial lung disease (ILD), a known complication of EGFR TKI therapy.<sup>42</sup> Patients who develop ILD cannot continue EGFR TKI therapy, and thus, cannot receive OSI if they acquire the T790M mutation. Furthermore, the survival of patients with EGFR-mutated NSCLC is generally longer<sup>43</sup> than those with EGFR wild-type NSCLC. It is therefore important that the risk of ILD, and any other AEs, in first-line treatment is reduced. In RELAY+, ILD events were reported by two patients (2.4%), an occurrence similar to that observed in the RELAY Japanese and East Asian populations with RAM plus ERL (one patient [1.8%] and three patients [1.8%], respectively), and lower than that observed with PL plus ERL (five patients [4.8%] and six patients [3.5%], respectively).<sup>18,19</sup> In a phase 3 study comparing GEF and standard chemotherapy in Japanese patients with EGFR-mutated NSCLC (NEJ002), the incidence of ILD with GEF monotherapy was 5.3% (six of 114 patients),<sup>27</sup> indicating RAM plus GEF in RELAY+, or RAM plus ERL in RELAY, did not increase the number of ILD events.

In this patient cohort, the presence of a TP53 alteration at baseline, as well as a detectable EGFR mutation in ctDNA, was confirmed to be associated

with a poor prognosis. Suppression of the EGFR-activating mutation allele frequency at cycle 4 with RAM plus GEF was not associated with prognosis. Emergence of the T790M mutation can lead to acquired resistance to EGFR TKIs resulting in treatment failure.<sup>9,10,44</sup> Tumor-derived elements isolated from liquid biopsy samples provide a less invasive alternative to tumor biopsies.<sup>45</sup> By Guardant360 NGS, the post-progression T790M rates with RAM plus GEF were 48.0% (12 of 25 patients) and 81.0% (13 of 16 patients) for patients with an NGS result at baseline and at 30-day follow-up and for those with an NGS result at 30-day follow-up containing an EGFR-activating mutation, respectively. These data suggest that treatment with an EGFR TKI targeted therapy, such as OSI, continues to be a subsequent treatment option.

RELAY+ implemented a relevant treatment combination using GEF for a study population of East Asian patients.<sup>25</sup> This study was further strengthened with the addition of the exploratory liquid biopsy study to assess treatment-emergent T790M mutation rates. This study was limited by the open-label exploratory design without a control or comparator group, and the exploratory liquid biopsy addendum was limited to patients with a valid baseline sample. The study is ongoing, and the evaluation of RAM plus OSI after acquisition of the T790M mutation is still to be determined.

## Conclusions

RELAY+ revealed a favorable benefit-risk profile for RAM plus GEF in the first-line treatment of East Asian patients with EGFR-mutated NSCLC. The addition of RAM to GEF did not result in new or unexpected safety findings. RAM plus GEF provides an alternative treatment option for patients with EGFR-mutated NSCLC whose preferred first-generation EGFR TKI is GEF. Further treatment with RAM plus OSI after T790M mutation acquisition is being studied.

## CRedit Authorship Contribution Statement

**Makoto Nishio:** Conceptualization, Investigation, Writing - review & editing.

**Kazuto Nishio:** Conceptualization, Data curation, Writing - review & editing.

**Martin Reck:** Project administration, Supervision, Validation, Visualization, Writing - review & editing.

**Edward B. Garon:** Resources, Writing - review & editing.

**Fumio Imamura, Tomoya Kawaguchi, Hiroyuki Yamaguchi, Satoshi Ikeda, Katsuya Hirano:** Investigation, Writing - review & editing.

**Carla Visseren-Grul, Matteo Ceccarelli:** Conceptualization, Investigation, Project administration, Writing - review & editing.

**Sameera R. Wijayawardana, Annamaria Zimmermann:** Data curation, Investigation, Methodology, Software, Writing - review & editing.

**Tomoko Matsui, Sotaro Enatsu:** Conceptualization, Writing - review & editing.

**Kazuhiko Nakagawa:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing - review & editing.

## Data Sharing Statement

Eli Lilly and Company 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 United States and the 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, 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](http://www.vivli.org).

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## 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](http://www.jtocrr.org) and at <https://doi.org/10.1016/j.jtocrr.2022.100303>.

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