ORIGINAL ARTICLE

Lazertinib Versus Osimertinib in Previously Untreated *EGFR*-Mutant Advanced NSCLC: A Randomized, Double-Blind, Exploratory Analysis From MARIPOSA

Se-Hoon Lee, MD, PhD,[a,*] Shun Lu, MD, PhD,[b] Hidetoshi Hayashi, MD, PhD,[c] Enriqueta Felip, MD, PhD,[d] Alexander I. Spira, MD, PhD,[e] Nicolas Girard, MD, PhD,[f] Yu Jung Kim, MD, PhD,[g] Yurii Ostapenko, MD, PhD,[h] Pongwut Danchaivijitr, MD,[i] Baogang Liu, MD,[j] Adlinda Alip, MD,[k] Ernesto Korbenfeld, MD,[l] Josiane Mourão Dias, MD,[m] Ki Hyeong Lee, MD,[n] Hailin Xiong, MD,[o] Soon Hin How, MD,[p] Ying Cheng, MD,[q] Gee-Chen Chang, MD, PhD,[r] James Chih-Hsin Yang, MD, PhD,[s] Benjamin Besse, MD, PhD,[t] Michael Thomas, MD,[u] Sujay Shah, MD,[v] Mahadi Baig, MD, MHCM,[w] Joshua C. Curtin, PhD,[v] Jiarui Zhang, PhD,[v] John Xie, PhD,[w] Tao Sun, PhD,[w] Seema Sethi, DO,[v] Miao Wang, MD, PhD,[x] Elizabeth Fennema, MA,[x] Mahesh Daksh, PhD,[w] Mariah Ennis, MS,[v] Joshua M. Bauml, MD,[v] Byoung Chul Cho, MD, PhD[y]

[a]*Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[b]*Shanghai Lung Cancer Center, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, People's Republic of China*
[c]*Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan*
[d]*Medical Oncology Service, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, Barcelona, Spain*
[e]*Virginia Cancer Specialists, Fairfax, Virginia*
[f]*Institut du Thorax Curie-Montsouris, Paris, France; Paris-Saclay University, UVSQ, Versailles, France*
[g]*Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea*
[h]*National Cancer Institute, Kyiv, Ukraine*
[i]*Siriraj Hospital, Mahidol University Bangkok Noi Campus, Bangkok, Thailand*
[j]*Harbin Medical University Cancer Hospital, Harbin, People's Republic of China*
[k]*Clinical Oncology Department, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia*
[l]*British Hospital of Buenos Aires – Central British Hospital, Buenos Aires, Argentina*
[m]*Department of Medical Oncology, Barretos Cancer Hospital, São Paulo, Brazil*
[n]*Medical Department, Chungbuk National University Hospital, Cheongju, Republic of Korea*
[o]*Huizhou Municipal Central Hospital of Guangdong Province, Huizhou, People's Republic of China*
[p]*International Islamic University Malaysia (IIUM) Medical Specialist Centre, Pahang, Malaysia*
[q]*Jilin Cancer Hospital, Changchun, People's Republic of China*
[r]*Division of Pulmonary Medicine, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan; Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan; School of Medicine, Chung Shan Medical University, Taichung, Taiwan*
[s]*National Taiwan University Cancer Center, Taipei, Taiwan*
[t]*Paris-Saclay University, Institut Gustave Roussy, Villejuif, France*
[u]*Department of Thoracic Oncology, Thoraxklinik, Heidelberg University Hospital and National Center for Tumor Diseases, NCT Heidelberg, a partnership between DKFZ and Heidelberg University Hospital, Heidelberg, Germany; Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany*

***Corresponding author.**

Presented at World Conference on Lung Cancer (WCLC) Annual Meeting, September 7 to 10, 2024, San Diego, CA, USA.

Address for correspondence: Se-Hoon Lee, MD, PhD, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-Ro, Gangnam-gu, Seoul 06351, Republic of Korea. E-mail: sehoon.lee119@gmail.com

Cite this article as: Lee SH, Lu S, Hayashi H, et al. Lazertinib versus osimertinib in previously untreated *EGFR*-mutant advanced NSCLC: a randomized, double-blind, exploratory analysis from MARIPOSA. *J Thorac Oncol*. 2025;20:1655-1668.

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2025.06.030

[v]Johnson & Johnson, Spring House, Pennsylvania
[w]Johnson & Johnson, Raritan, New Jersey
[x]Johnson & Johnson, San Diego, California
[y]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Received 28 February 2025; revised 25 June 2025; accepted 28 June 2025
Available online - 3 July 2025

ABSTRACT

Introduction: Lazertinib is a central nervous system–penetrant, third-generation *EGFR* tyrosine kinase inhibitor (TKI) that was selected for combination with amivantamab due to its relatively low rates of wild-type *EGFR* toxicities. In the phase 3 MARIPOSA study, amivantamab plus lazertinib (amivantamab-lazertinib) significantly improved progression-free survival (PFS; $p < 0.001$) versus osimertinib in participants with treatment-naive *EGFR*-mutant advanced NSCLC. A lazertinib monotherapy arm was included to assess the contribution of components in the combination. This is the first randomized, double-blind comparison of two third-generation EGFR TKIs, lazertinib and osimertinib.

Methods: In MARIPOSA, 1074 participants were randomized 2:2:1 to receive amivantamab-lazertinib (n = 429), osimertinib monotherapy (n = 429), or lazertinib monotherapy (n = 216). This exploratory analysis compared the efficacy and safety of lazertinib and osimertinib.

Results: At a median follow-up of 22.0 months, median PFS was 18.5 months for lazertinib versus 16.6 months for osimertinib (hazard ratio = 0.98, 95% confidence interval: 0.79–1.22; $p = 0.86$). PFS results were comparable between arms among predefined subgroups. Among participants with measurable disease at baseline, objective response rate was 83% for lazertinib versus 85% for osimertinib, with a median duration of response among confirmed responders of 16.6 months versus 16.8 months, respectively. Median overall survival was not reached for both arms (hazard ratio = 1.00, 95% confidence interval: 0.73–1.38) at the interim analysis. Adverse events for both arms were mostly grades 1 to 2 and frequently related to EGFR inhibition. Lazertinib was associated with lower rates of QT interval prolongation versus osimertinib.

Conclusions: Lazertinib demonstrated comparable efficacy and safety to osimertinib, including in predefined subgroups.

Keywords: *EGFR*-mutant NSCLC; First-line treatment; Lazertinib; Osimertinib; Tyrosine kinase inhibitor

Introduction

Activating exon 19 deletions (Ex19del) and exon 21 L858R (L858R) substitutions in the *EGFR* gene represent 85% to 90% of the *EGFR* mutations found in NSCLC.[1,2] Third-generation EGFR tyrosine kinase inhibitors (TKIs), including lazertinib, osimertinib, aumolertinib, and furmonertinib, are frequently used to treat *EGFR*-mutant advanced NSCLC.[3] Lazertinib and osimertinib have separately demonstrated significantly improved progression-free survival (PFS) versus first-generation EGFR TKIs in the phase 3 LASER301 and FLAURA studies, respectively.[4,5] The overall frequency of treatment-emergent adverse events (TEAEs) was similar between first- and third-generation EGFR TKIs. In FLAURA, rates of rash were lower with osimertinib (58%) versus gefitinib or erlotinib (78%).[4] In LASER301, rates of diarrhea were lower with lazertinib (26%) versus gefitinib (39%).[5]

Lazertinib is a highly selective, central nervous system–penetrant, third-generation EGFR TKI that has demonstrated efficacy in advanced NSCLC with activating *EGFR* mutations and T790M resistance mutations.[6,7] Lazertinib is highly selective for mutant *EGFR*, as evidenced by relatively low rates of wild-type *EGFR* toxicities and a low risk of QT interval prolongation or cardiomyopathy, potentially due to its minimal inhibition of HER2 (k_{inact}/K_I 6310 ± 440 versus 14,000 ± 600 M^{-1} s^{-1} for lazertinib and osimertinib, respectively).[5,8,9] In LASER301, grade 3 or higher QT interval prolongation was observed in two participants (1%) in the lazertinib arm, and there were no clinically significant decreases found in left ventricular ejection fraction (LVEF).[5] Among participants treated with osimertinib in the FLAURA study, QT interval prolongation was reported in 28 participants (10%) (grade 3 or higher events in six [2%] participants), and LVEF decreased by greater than or equal to 10%, with a drop to less than 50% in eight participants (3%).[4]

In the primary analysis of the phase 3 MARIPOSA study (ClinicalTrials.gov identifier: NCT04487080), amivantamab plus lazertinib (amivantamab-lazertinib) demonstrated significantly longer PFS (23.7 versus 16.6 mo, hazard ratio [HR] = 0.70, 95% confidence interval [CI]: 0.58–0.85, $p < 0.001$) and prolonged OS versus osimertinib among treatment-naive participants with *EGFR*-mutant advanced NSCLC.[10] Based on these results,

amivantamab-lazertinib was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a first-line treatment for patients with advanced NSCLC with common *EGFR* mutations (Ex19del or L858R).[12,13] A double-blind lazertinib monotherapy arm was included in MARIPOSA to assess the contribution of components in the combination.

In this exploratory analysis of the MARIPOSA study, we compared the efficacy and safety of lazertinib monotherapy with osimertinib monotherapy in participants with previously untreated *EGFR*-mutant advanced NSCLC from the primary analysis (clinical cutoff: August 11, 2023). This is the first study to prospectively evaluate two third-generation EGFR TKIs in a randomized, double-blind fashion.

Materials and Methods

Participants

MARIPOSA enrolled participants aged 18 years or older with treatment-naive locally advanced or metastatic NSCLC harboring common *EGFR* mutations (Ex19del or L858R), with an Eastern Cooperative Oncology Group performance status score of 0 or 1. Participants with asymptomatic or previously treated and stable brain metastases were eligible. Details regarding the study design and methodology have previously been reported.[10]

Study Design and Treatment

Participants were randomly assigned in a 2:2:1 ratio to receive amivantamab-lazertinib, osimertinib monotherapy, or lazertinib monotherapy (Supplementary Fig. 1). Osimertinib 80 mg and lazertinib 240 mg were taken orally daily and administered in a double-blind manner. Randomization was stratified by *EGFR* mutation type (Ex19del or L858R), Asian race (yes or no), and history of brain metastases (yes or no).

Study Oversight

The study was conducted in accordance with principles of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Council for Harmonisation), applicable regulatory requirements, and Janssen Research & Development's bioethics policy. The study was designed by the sponsor's representatives, who were responsible for data collection and analysis, and data interpretation in collaboration with the authors. The first draft of the manuscript was written by the authors, with medical writing assistance funded by the sponsor and conducted in accordance with Good Publication Practice guidelines. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

End Points and Assessments

In the primary analysis of MARIPOSA, the primary end point was PFS by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors, version 1.1. Overall survival (OS) was a key secondary end point. Additional end points included objective response rate (ORR), duration of response (DoR), time to symptomatic progression (TTSP), PFS after first subsequent therapy (PFS2), safety, time to treatment discontinuation (TTD), and time to subsequent therapy (TTST). In this analysis of the osimertinib and lazertinib arms, all end points were considered exploratory and were analyzed similarly to the primary analysis, except without alpha allocation. End point definitions have been reported previously and are provided in the protocol.[10]

Disease assessments by magnetic resonance imaging (MRI) and computed tomography were performed within 28 days before randomization at baseline, then every 8 weeks (±1 wk) for the first 30 months, and then every 12 weeks (±1 wk) thereafter until BICR-confirmed disease progression. Serial brain imaging with MRI was required for all participants. The imaging schedule has been reported previously.[10] Adverse events (AEs), vital signs, and laboratory tests were monitored at each visit and graded using the Common Terminology Criteria for Adverse Events, version 5.0, of the National Cancer Institute.

Statistical Analysis

Efficacy outcomes were analyzed in all participants who had undergone randomization. Safety outcomes were analyzed in all participants in the efficacy population who had received at least one dose of any study treatment.

PFS was analyzed using the Kaplan-Meier method, with medians, 95% CIs, and number of events summarized. Significance was assessed using a log-rank test stratified by mutation type (Ex19del versus L858R), race (Asian versus non-Asian), and history of brain metastases (present versus absent). The HRs and 95% CI were calculated from a stratified Cox regression model without adjustment for multiplicity and should not be used to infer definitive treatment effects. All p values are nominal.

All results reported here are based on the exploratory analysis of lazertinib versus osimertinib, with data collected by the clinical cutoff date of the primary analysis, August 11, 2023.

Results

Participants

From November 2020 to May 2022, 1375 participants were screened and 1074 underwent randomization

(429 to amivantamab-lazertinib, 429 to osimertinib, and 216 to lazertinib).[10] A total of 1062 participants received at least one dose of the study treatment. Baseline demographics and clinical characteristics of the participants were well balanced among the lazertinib and osimertinib arms (Table 1). Most participants were women (63% in the lazertinib arm and 59% in the osimertinib arm), were Asian (59% in both the lazertinib and osimertinib arms), did not have a history of tobacco use (66% in the lazertinib arm and 69% in the osimertinib arm), and had Ex19del mutations (61% in the lazertinib arm and 60% in the osimertinib arm). Furthermore, 40% of the participants in both arms had a history of brain metastases.

At a median follow-up of 22.0 months, median duration of the study treatment was 17.1 (range; 0.4–32.1) months for lazertinib and 18.0 (range: 0.2–32.7) months for osimertinib. At the clinical cutoff date (August 11, 2023), 106 participants (50%) in the lazertinib arm and 213 participants (50%) in the

Table 1. Demographic and Baseline Disease Characteristics

Characteristics	Osimertinib (n = 429)	Lazertinib (n = 216)
Age		
Median (range), y	63 (28-88)	63 (31-87)
Distribution, n (%)		
<65 y	237 (55)	119 (55)
65 to <75 y	139 (32)	79 (37)
≥75 y	53 (12)	18 (8)
Female sex, n (%)	251 (59)	136 (63)
Race or ethnic group, n (%)[a]		
Asian	251 (59)	128 (59)
White	165 (38)	79 (37)
American Indian or Alaska Native	7 (2)	4 (2)
Black or African American	3 (1)	4 (2)
Native Hawaiian or Pacific Islander	1 (0.2)	0
Multiple	1 (0.2)	0
Unknown	1 (0.2)	1 (0.5)
Body weight		
Median (range), kg	62.4 (35-109)	60.5 (41-118)
Distribution, n (%)		
<80 kg	368 (86)	197 (91)
≥80 kg	61 (14)	19 (9)
ECOG PS score, n (%)[b]		
0	149 (35)	76 (35)
1	280 (65)	140 (65)
History of tobacco use, n (%)		
No	295 (69)	143 (66)
Yes	134 (31)	73 (34)
Median time from initial diagnosis to randomization (range), mo	1.4 (0.3-162.8)	1.3 (0.2-197.3)
Median time from diagnosis of metastatic disease to randomization (range), mo	1.2 (0.1-11.7)	1.2 (0.2-9.2)
Histologic type, n (%)		
Adenocarcinoma	415 (97)	212 (98)
Large cell carcinoma	0	0
Squamous cell carcinoma	5 (1)	2 (1)
Other[c]	9 (2)	2 (1)
Not reported	0	0
History of brain metastases, n (%)	172 (40)	86 (40)
EGFR mutation, n (%)		
Ex19del	257 (60)	131 (61)
L858R	172 (40)	85 (39)

Note: Percentages may not sum to 100 due to rounding.
[a]Race or ethnic group was reported by the participants.
[b]ECOG PS scores range from 0 to 5, with higher scores indicating greater disability.
[c]Other histologic types included are as follows: adenocarcinoma and squamous cell carcinoma, lepidic adenocarcinoma, non-small cell carcinoma, pleomorphic carcinoma, and unknown.
ECOG PS, Eastern Cooperative Oncology Group performance status; Ex19del, exon 19 deletion; L858R, exon 21 L858R.

osimertinib arm were still receiving their assigned treatment. The most common reasons for treatment discontinuation were progressive disease (72 [34%] participants for lazertinib; 154 [36%] participants for osimertinib) and AEs (29 [14%] participants for lazertinib; 50 [12%] participants for osimertinib).

Efficacy

Median PFS determined by BICR was 18.5 months (95% CI: 14.8–20.1) in the lazertinib arm versus 16.6 months (95% CI: 14.8–18.5) in the osimertinib arm (Fig. 1*A*). The HR for disease progression or death was 0.98 (95% CI: 0.79–1.22) ($p = 0.86$). At 18 months, 52% (95% CI: 44–58) of the participants in the lazertinib arm and 48% (95% CI: 43–53) of the participants in the osimertinib arm were alive and progression free; corresponding values at 24 months were 35% (95% CI: 27–42) and 34% (95% CI: 28–39), respectively (Table 2).

Median PFS with lazertinib versus osimertinib was comparable among prespecified subgroups (Fig. 1*B*), including participants with brain metastases who demonstrated a median PFS of 16.4 months (95% CI: 12.9–19.4) in the lazertinib arm versus 13.0 months (95% CI: 12.2–16.4) in the osimertinib arm (HR = 0.90, 95% CI: 0.65–1.25, $p = 0.54$; Supplementary Fig. 2A). Similarly, PFS was comparable between arms for participants with high-risk factors, such as baseline detectable circulating tumor DNA (ctDNA; Supplementary Fig. 2B) and the presence of *TP53* co-mutations (Supplementary Fig. 2C).

The ORR was 83% (95% CI: 77–88) in the lazertinib arm and 85% (95% CI: 81–88) in the osimertinib arm (Table 2). The confirmed response rate was 75% (95% CI: 68–80) in the lazertinib arm and 76% (95% CI: 71–80) in the osimertinib arm, with a median DoR among confirmed responders of 16.6 months (95% CI: 14.8–20.2) and 16.8 months (95% CI: 14.8–18.5), respectively. The proportion of participants with ongoing responses at the time of clinical cutoff was 48% in both the lazertinib and osimertinib arms.

Comparable results between the two arms were also found for other exploratory end points, including TTSP, TTD, TTST, and PFS2, and the secondary end point of OS. Median TTSP was not estimable (NE; 95% CI: NE–NE) for the lazertinib arm and 29.3 months (95% CI: 25.3–NE) for the osimertinib arm (HR = 0.85, 95% CI: 0.65–1.13, $p = 0.27$; Fig. 2*A*). Post-progression end points, such as TTD, TTST, and PFS2, are summarized in Supplementary Table 1. Among participants who discontinued their study treatment, 77% in the lazertinib arm and 73% in the osimertinib arm started a subsequent therapy (Supplementary Table 2). Among those participants, the most common first subsequent therapy class was chemotherapy alone in both arms. At the time of interim OS analysis, median OS was NE for both arms (HR = 1.00, 95% CI: 0.73–1.38, $p = 1.00$; Fig. 2*B*). The percentage of participants who were alive at 18 and 24 months was 78% and 71% in the lazertinib arm and 79% and 69% in the osimertinib arm, respectively.

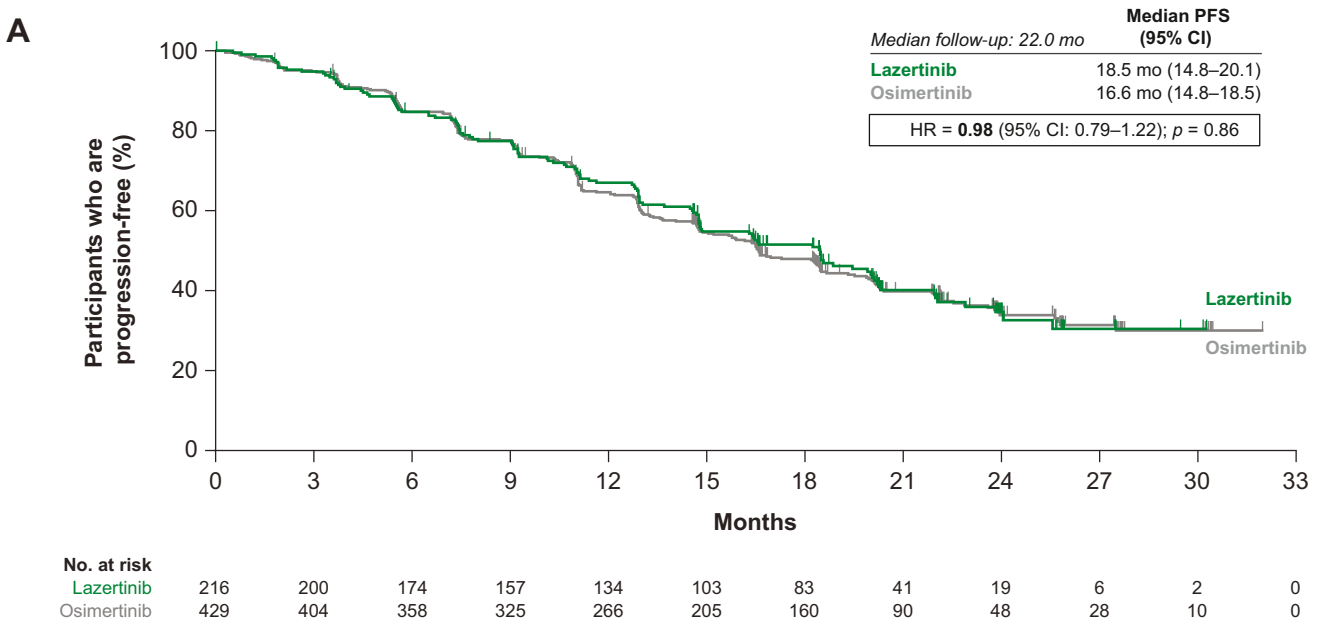
Safety

The safety profiles for lazertinib and osimertinib were consistent with previous reports,[4,5] with most individual AEs being grade 1 or 2 (Table 3). The most common TEAEs for lazertinib and osimertinib were rash (45% versus 31%), diarrhea (32% versus 44%), and paronychia (29% versus 28%), respectively. Grade 3 or higher AEs were reported in 46% of the participants treated with lazertinib and 43% of the participants treated with osimertinib. Serious AEs were reported in 35% of the participants treated with lazertinib and 33% of the participants treated with osimertinib (Table 3 and Supplementary Table 3).

The grouped term venous thromboembolism (VTE), which included pulmonary embolism, deep vein thrombosis, and thrombosis, among others, was reported in 14% of the participants in the lazertinib arm and 9% of those in the osimertinib arm (Supplementary Table 4). The grouped term interstitial lung disease, which included pneumonitis and interstitial lung disease, was reported in 3% of the participants for both arms.

Lazertinib had lower rates of QT interval prolongation versus osimertinib. The percentage of participants with a QT interval greater than 450 msec was 9% for participants receiving lazertinib versus 17% for participants receiving osimertinib (Fig. 3*A*). No participants in the lazertinib arm had a QT interval greater than 500 msec compared with 0.7% of participants in the osimertinib arm. The percentage of participants with LVEF less than the lower limit of normal and with more than 10% absolute decrease from baseline was 1% in the lazertinib arm versus 4% in the osimertinib arm (Fig. 3*B*).

In the lazertinib arm, AEs leading to dose interruptions were reported in 92 participants (43%), dose reductions in 27 participants (13%), and discontinuation of the study treatment in 28 participants (13%); the corresponding numbers in the osimertinib arm were 165 (39%), 23 (5%), and 58 (14%), respectively (Supplementary Table 5). Discontinuations due to treatment-related AEs were comparable and low for both lazertinib and osimertinib (5% and 3%, respectively; Supplementary Table 6). AEs leading to death were similarly comparable and low in the lazertinib and osimertinib arms (6% and 7%, respectively; Table 3 and Supplementary Table 7).



B

Subgroup	Events/N Lazertinib	Events/N Osimertinib	HR (95% CI)
All randomized participants	121/216	252/429	0.98 (0.79–1.22)
Age category			
<65 years	67/119	153/237	0.83 (0.62–1.11)
≥65 years	54/97	99/192	1.20 (0.86–1.67)
<75 years	113/198	220/376	0.99 (0.79–1.25)
≥75 years	8/18	32/53	0.83 (0.38–1.80)
Sex			
Female	68/136	140/251	0.88 (0.66–1.18)
Male	53/80	112/178	1.18 (0.85–1.63)
Race			
Asian	72/128	144/251	1.02 (0.77–1.35)
Non-Asian	49/87	108/177	0.93 (0.66–1.30)
Weight category			
<80 kg	107/197	209/368	0.99 (0.78–1.25)
≥80 kg	14/19	43/61	1.01 (0.55–1.85)
ECOG PS score			
0	42/76	76/149	1.19 (0.81–1.73)
1	79/140	176/280	0.88 (0.68–1.15)
History of smoking			
Yes	42/73	79/134	0.95 (0.66–1.39)
No	79/143	173/295	0.98 (0.75–1.27)
History of brain metastases			
Yes	54/86	111/172	0.90 (0.65–1.25)
No	67/130	141/257	1.01 (0.75–1.35)
EGFR mutation			
Ex19del	73/131	142/257	1.03 (0.78–1.37)
L858R	48/85	110/172	0.91 (0.65–1.28)

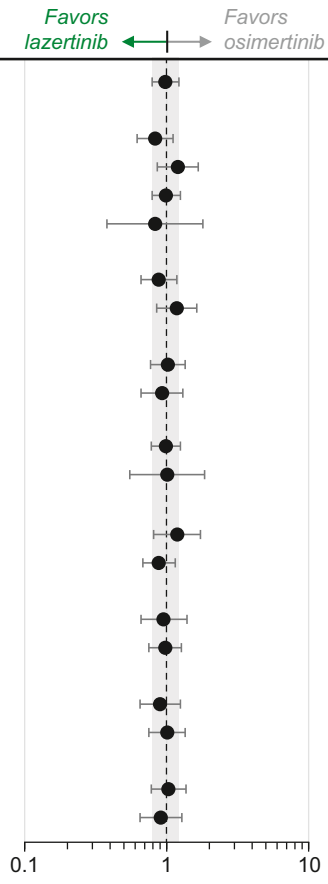


Figure 1. PFS by BICR (*A*) among the efficacy population and (*B*) among predefined subgroups. BICR, blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Ex19del, exon 19 deletion; HR, hazard ratio; L858R, exon 21 L858R; PFS, progression-free survival.

Table 2. Key Efficacy End Points

End Point	Osimertinib (n = 429)	Lazertinib (n = 216)	Treatment Effect (95% CI)	*p* Value
PFS[a]				
Median (95% CI), mo	16.6 (14.8-18.5)	18.5 (14.8-20.1)	HR = 0.98 (0.79-1.22)	0.86
Percentage of participants alive and progression-free (95% CI)				
At 12 mo	65 (60-69)	67 (60-73)		
At 18 mo	48 (43-53)	52 (44-58)		
At 24 mo	34 (28-39)	35 (27-42)		
OS				
Median (95% CI), mo	NE	NE	HR = 1.00 (0.73-1.38)	1.00
Percentage of participants alive (95% CI)				
At 12 mo	88 (85-91)	86 (81-90)		
At 18 mo	79 (75-83)	78 (71-83)		
At 24 mo	69 (64-74)	71 (64-78)		
ORR (95% CI), %[b]	85 (81-88)	83 (77-88)	Odds ratio = 0.88 (0.56-1.37)[c]	0.57
Best response[d]				
CR	15 (4)	9 (4)		
PR	335 (81)	168 (79)		
SD	42 (10)	23 (11)		
PD	11 (3)	9 (4)		
NE	11 (3)	5 (2)		
DoR[b]				
Median (95% CI)[e], mo	16.8 (14.8-18.5)	16.6 (14.8-20.2)		

Note: The efficacy population included all the participants who had undergone randomization.
[a]PFS was assessed by BICR.
[b]The objective response (CR or PR) and response duration were assessed by BICR. Included in the analysis were 214 participants with measurable disease at baseline in the lazertinib arm and 414 participants with measurable disease at baseline in the osimertinib arm.
[c]The odds ratio was from a logistic regression model stratified by *EGFR* mutation type, Asian race, and history of brain metastasis; 95% CI widths have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.
[d]Confirmation was not required for CR and PR.
[e]Among confirmed responders.
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

Discussion

The lazertinib monotherapy arm was included in the phase 3 MARIPOSA study to assess the contribution of components for the amivantamab-lazertinib combination, making this the first study to compare two third-generation EGFR TKIs with a randomized, double-blind design. In this exploratory analysis, lazertinib demonstrated comparable PFS to osimertinib monotherapy (HR = 0.98, 95% CI: 0.79–1.22, $p = 0.86$), which was consistent among predefined subgroups and participants with high-risk features, such as those with a history of brain metastases, detectable ctDNA at baseline, and *TP53* co-mutations. At the time of this analysis, interim OS data were immature to provide robust conclusions; however, early data suggest that survival outcomes seem comparable between lazertinib and osimertinib. Similar outcomes were consistently observed for lazertinib versus osimertinib across all other exploratory end points, including ORR, DoR, and TTSP, and post-progression end points, including TTD, TTST, and PFS2. These results reinforce that lazertinib has an efficacy profile comparable to that of other third-generation EGFR TKIs.

The safety profiles for lazertinib and osimertinib monotherapy were consistent with previous reports,[4,5] and most AEs were grade 1 or 2. Participants who received osimertinib experienced higher rates of diarrhea (44% versus 32%) and thrombocytopenia (20% versus 9%) compared with those who received lazertinib. Participants who received lazertinib experienced higher rates of rash (45% versus 31%), muscle spasms (23% versus 7%), alanine aminotransferase increase (23% versus 13%), dermatitis acneiform (21% versus 13%), aspartate aminotransferase increase (21% versus 14%), and paresthesia (15% versus 6%) compared with osimertinib. VTEs were comparable in the lazertinib and osimertinib arms (14% versus 9%), and most VTEs occurred after the first 4 months of treatment in both arms. The incidence of VTEs was markedly lower than that observed with amivantamab-lazertinib.[10] Recent studies have revealed that the combination of amivantamab and osimertinib is also associated with VTEs.[14] As anticipated due to its minimal inhibition of HER2,[8,9] the incidence of QT interval prolongation and risk of cardiomyopathy were lower with lazertinib than

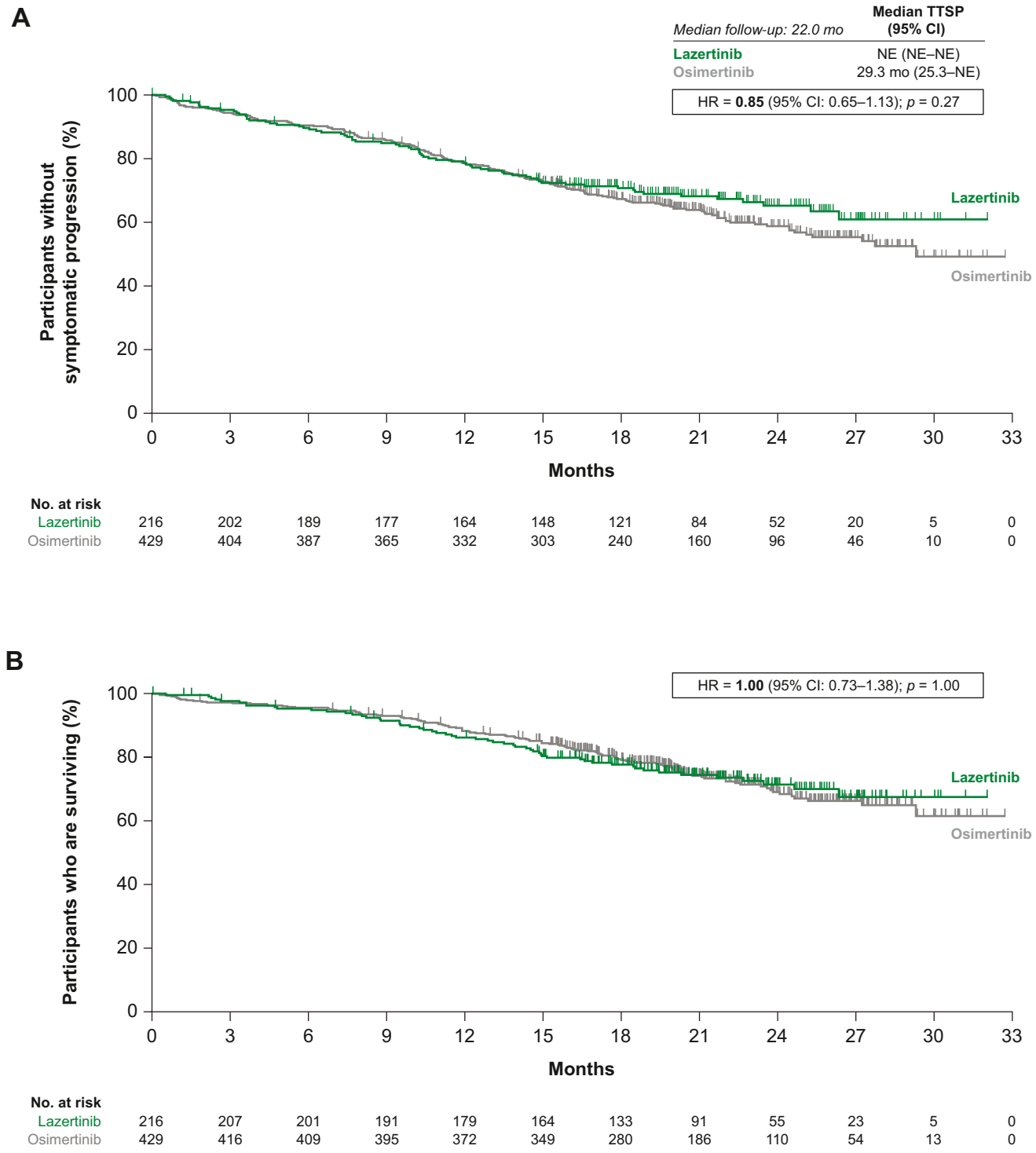


Figure 2. (*A*) TTSP[a] and (*B*) interim OS.[b] [a]Time from randomization to first onset of new/worsening of lung cancer symptoms requiring a change in therapy, clinical intervention, or death. [b]Time from randomization until the date of death due to any cause. CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; TTSP, time to symptomatic progression.

with osimertinib. Treatment-related AEs leading to discontinuations were comparable and low for both lazertinib and osimertinib (5% and 3%, respectively). These results demonstrate that lazertinib has a safety profile suitable for combination with amivantamab.

In a retrospective, real-world analysis of patients with NSCLC who received osimertinib from May 2016 to April 2023 (N = 1126), osimertinib-related cardiac dysfunction was observed in approximately 5% of patients. This is similar to the 6% rate reported by the FDA

Table 3. Safety Profile

Event, n (%)	Osimertinib (n = 428)		Lazertinib (n = 213)	
Any AE	425 (99)		213 (100)	
Grade ≥3 AEs	183 (43)		97 (46)	
Serious AEs	143 (33)		75 (35)	
AEs leading to death	31 (7)		12 (6)	
Any AE leading to:				
Interruption of any agent	165 (39)		92 (43)	
Reduction of any agent	23 (5)		27 (13)	
Discontinuation of any agent	58 (14)		28 (13)	
Most common TEAEs (≥15%) by preferred term[a]	All grades	Grade ≥3	All grades	Grade ≥3
Diarrhea	190 (44)	3 (1)	68 (32)	4 (2)
Rash	131 (31)	3 (1)	95 (45)	4 (2)
Paronychia	121 (28)	2 (0.5)	61 (29)	2 (1)
COVID-19	103 (24)	9 (2)	42 (20)	3 (1)
Anemia	91 (21)	7 (2)	43 (20)	3 (1)
Stomatitis	90 (21)	1 (0.2)	38 (18)	1 (0.5)
Cough	88 (21)	0	37 (17)	1 (0.5)
Thrombocytopenia	84 (20)	5 (1)	20 (9)	1 (0.5)
Decreased appetite	76 (18)	6 (1)	31 (15)	1 (0.5)
Pruritus	73 (17)	1 (0.2)	36 (17)	0
Dyspnea	68 (16)	17 (4)	26 (12)	1 (0.5)
Leukopenia	66 (15)	0	15 (7)	0
Dry skin	60 (14)	1 (0.2)	38 (18)	0
Increased aspartate aminotransferase	58 (14)	5 (1)	45 (21)	3 (1)
Nausea	58 (14)	1 (0.2)	38 (18)	1 (0.5)
Increased alanine aminotransferase	57 (13)	8 (2)	50 (23)	6 (3)
Constipation	55 (13)	0	37 (17)	1 (0.5)
Dermatitis acneiform	55 (13)	0	45 (21)	0
Headache	54 (13)	0	39 (18)	1 (0.5)
Asthenia	46 (11)	4 (1)	31 (15)	4 (2)
Muscle spasms	32 (7)	0	50 (23)	1 (0.5)
Paresthesia	25 (6)	0	33 (15)	1 (0.5)

Note: The safety population included all the participants who had undergone randomization and received ≥1 dose of any study treatment.
[a]Events in this category are listed according to decreasing incidence in the osimertinib arm.
AE, adverse event; TEAE, treatment-emergent adverse event.

Adverse Event Reporting System. Risk factors significantly associated with developing osimertinib-related cardiotoxicity included older age, history of heart failure, and atrial fibrillation. Even after adjusting for age in this real-world analysis, patients who developed osimertinib-related cardiotoxicity had a significantly higher risk of mortality ($p = 0.026$).[15] Lazertinib may be a more suitable treatment option and combination partner for patients with preexisting cardiac conditions or when there are concerns for enhanced cardiotoxicity, including older age or comorbidities, such as hypertension or diabetes.

The findings from this exploratory analysis build on the efficacy and safety data regarding lazertinib previously demonstrated in the phase 3 LASER301 study among treatment-naive participants with *EGFR*-mutant advanced NSCLC. In that study, lazertinib significantly improved PFS versus gefitinib (20.6 mo versus 9.7 mo; HR = 0.45, 95% CI: 0.34–0.58, $p < 0.001$). This benefit was observed across all participant subgroups (Ex19del, L858R, Asian, and non-Asian).[5]

Combination therapy is an important treatment strategy to improve on the current outcomes with first-line EGFR TKI monotherapy. First-line treatment with osimertinib has demonstrated a median PFS of approximately 1.5 years and an OS of approximately 3 years, indicating that new treatment options are needed to prolong survival and circumvent resistance mechanisms observed in the first-line setting.[4,16] Approximately 25% to 40% of patients do not receive a second-line therapy, emphasizing the need to use the most effective treatment first.[17–19] In addition, acquired resistance to third-generation TKIs caused by diverse and polyclonal mechanisms (most frequently *EGFR* and *MET* alterations) is nearly inevitable.[20–22] The addition of amivantamab to lazertinib significantly reduced the incidence of *MET* amplifications and secondary *EGFR* resistance alterations in the first-line setting versus osimertinib, altering the spectrum and reducing the complexity of acquired resistance found with osimertinib.[23,24] In the primary analysis of the MARIPOSA study,

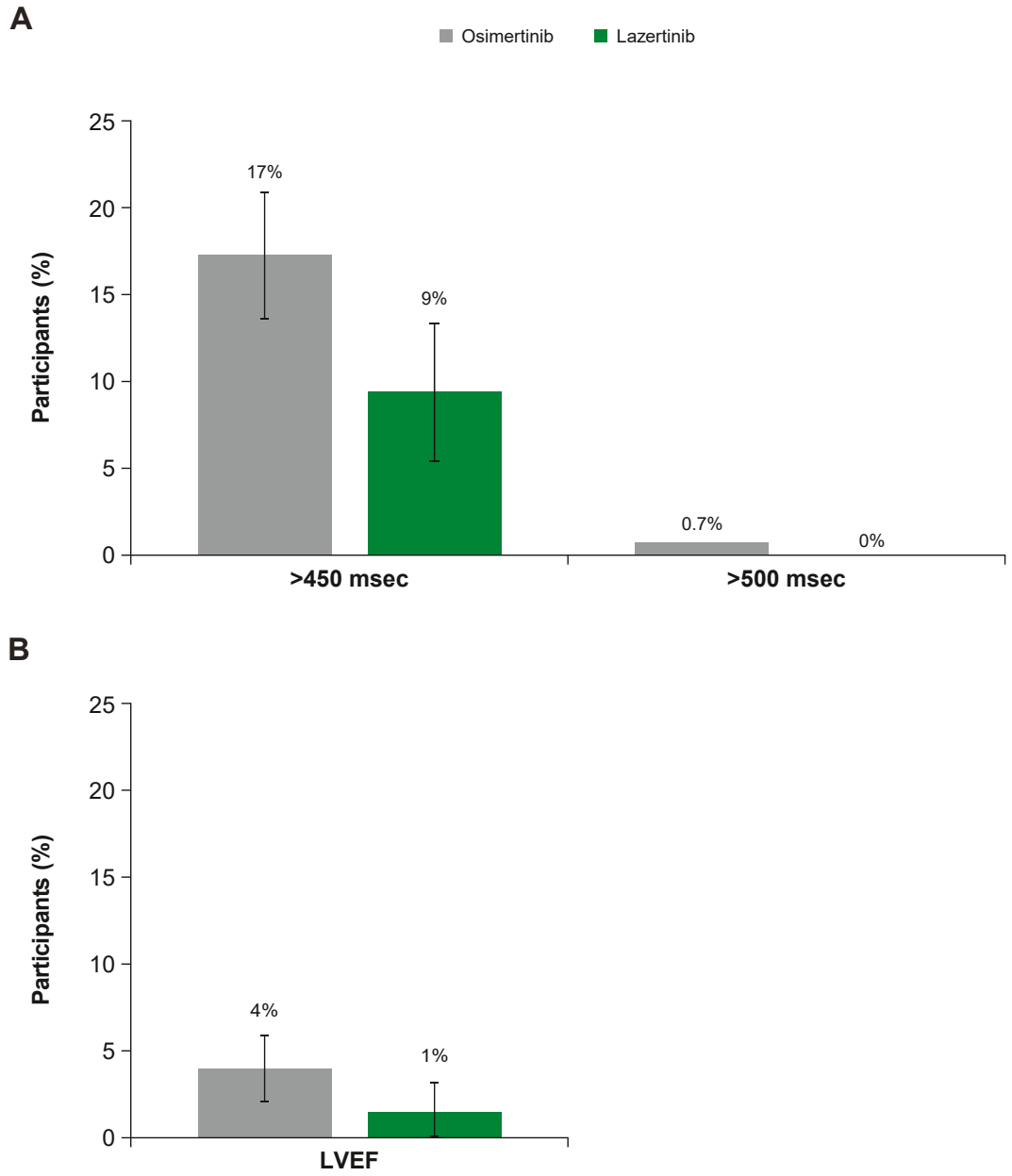


Figure 3. (*A*) Percentage of participants with QT interval >450 and >500 msec[a] and (*B*) percentage of participants with LVEF <LLN[b] and >10% absolute decrease from baseline. [a]Maximum postbaseline values. [b]LLN of LVEF was 45%. LLN, lower limit of normal; LVEF, left ventricular ejection fraction.

amivantamab-lazertinib significantly prolonged PFS (HR = 0.70, 95% CI: 0.58–0.85, $p < 0.001$) versus osimertinib monotherapy in treatment-naive participants with *EGFR*-mutant advanced NSCLC, leading to FDA and EMA approval for this patient population.[10–13]

In conclusion, the results from this exploratory analysis suggest that lazertinib has a comparable efficacy and safety profile to that of osimertinib. A similar degree of efficacy was observed in both arms across all exploratory end points, including in high-risk subgroups. The data from MARIPOSA indicate that lazertinib is a suitable and safe combination partner for amivantamab. Lazertinib in combination with amivantamab provides a multitargeted, chemotherapy-free regimen with efficacy that is superior to that of osimertinib in patients with *EGFR*-mutant advanced NSCLC, including those with high-risk features.

CRediT Authorship Contribution Statement

Se-Hoon Lee: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Shun Lu: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Hidetoshi Hayashi: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Enriqueta Felip: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Alexander I. Spira: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Nicolas Girard: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Yu Jung Kim: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Yurii Ostapenko: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Pongwut Danchaivijitr: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Baogang Liu: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Adlinda Alip: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Ernesto Korbenfeld: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Josiane Mourão Dias: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Ki Hyeong Lee: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Hailin Xiong: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Soon Hin How: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Ying Cheng: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Gee-Chen Chang: Data curation, Investigation, Validation, Writing – original draft, Writing – review and editing.

James Chih-Hsin Yang: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Benjamin Besse: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Michael Thomas: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Sujay Shah: Writing – original draft, Writing – review and editing.

Mahadi Baig: Writing – original draft, Writing – review and editing.

Joshua C. Curtin: Writing – original draft, Writing – review and editing.

Jiarui Zhang: Writing – original draft, Writing – review and editing.

John Xie: Writing – original draft, Writing – review and editing.

Tao Sun: Writing – original draft, Writing – review and editing.

Seema Sethi: Writing – original draft, Writing – review and editing.

Miao Wang: Writing – original draft, Writing – review and editing.

Elizabeth Fennema: Writing – original draft, Writing – review and editing.

Mahesh Daksh: Writing – original draft, Writing – review and editing.

Mariah Ennis: Writing – original draft, Writing – review and editing.

Joshua M. Bauml: Writing – original draft, Writing – review and editing.

Byoung Chul Cho: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Disclosure

Dr. Lee reports serving in a consulting or advisory role for Abion, AstraZeneca, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, IMBdx, ImmuneOncia, Janssen, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Takeda; receiving honoraria from Amgen, AstraZeneca/MedImmune, Bristol Myers Squibb, Merck Sharp & Dohme, Roche, and Yuhan Corporation; and receiving research funding from AstraZeneca, Lunit, and Merck Sharp & Dohme, outside of the current work.

Dr. Lu reports serving in a consulting or advisory role for AstraZeneca, Pfizer, Boehringer Ingelheim, Hutchison, Bristol Myers Squibb, Simcere Pharmaceutical Group, Zai Lab, GenomiCare, Yuhan Corporation, Roche, and Innovent Biologics; participating in a speakers bureau for AstraZeneca, Roche, Hansoh, and Hengrui Therapeutics; and receiving research funding from AstraZeneca, Hutchison MediPharma, Bristol Myers Squibb, Hengrui Therapeutics, BeiGene, Roche, Hansoh, and Lilly Suzhou Pharmaceutical, outside of the current work.

Dr. Hayashi reports serving in a consulting or advisory role for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo/UCB Japan, and Janssen; having patents, royalties, or other intellectual property with Sysmex; receiving honoraria from Ono Pharmaceutical, Bristol Myers Squibb Japan, Eli Lilly, Boehringer Ingelheim, AstraZeneca Japan, Chugai Pharma, Pfizer, Merck Sharp & Dohme, Novartis, Merck Serono, Amgen, Daiichi Sankyo/UCB Japan, Guardant Health, and Takeda; and receiving research funding from Ono Pharmaceutical, Boehringer Ingelheim, AstraZeneca, AbbVie, AC Medical, Astellas Pharma, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly Japan, EPS Associates, GlaxoSmithKline, Japan Clinical Research Operations, Kyowa Kirin, Merck Serono, Novartis, Otsuka, Parexel, Pfizer, PPD-SNBL, Quintiles, Taiho Pharmaceutical, Takeda, Yakult Honsha, Chugai Pharma, and Sysmex, outside of the current work.

Dr. Felip reports serving in a consulting or advisory role for Amgen, AstraZeneca, Bayer, Boehringer

Ingelheim, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi, Takeda, and Peptomyc; receiving speakers bureau fees from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Medscape, Merck Sharp & Dohme, PeerVoice, Pfizer, Roche, Takeda, and CME Outfitters; having other relationships with Grifols; and receiving research funding (institution) from Merck and Merck KGaA, outside of the current work.

Dr. Spira reports serving in a leadership role at NEXT Oncology Virginia; holding stock in Eli Lilly; receiving honoraria from CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen, Novartis, Bristol Myers Squibb, and Bayer; serving in a consulting or advisory role for Incyte, Amgen, Novartis, Mirati Therapeutics, Gritstone Oncology, Jazz Pharmaceuticals, Takeda, Janssen Research & Development, Mersana, Gritstone bio, Daiichi Sankyo/AstraZeneca, Regeneron, Array BioPharma, AstraZeneca/MedImmune, Merck, Bristol Myers Squibb, and Blueprint Medicines; and receiving research funding from LAM Therapeutics, Regeneron, Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, NewLink Genetics, Incyte, AbbVie, Ignyta, Trovagene, Takeda, MacroGenics, CytomX Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, Loxo, Arch Therapeutics, Gritstone bio, Plexxikon, Amgen, Daiichi Sankyo, ADCT, Janssen, Mirati Therapeutics, Rubius, Synthekine, Mersana, Blueprint Medicines, Alkermes, and Revolution Medicines, outside of the current work.

Dr. Girard reports serving in a consulting or advisory role for Roche, Eli Lilly, AstraZeneca, Novartis, Pfizer, Bristol Myers Squibb, Merck Sharp & Dohme, Takeda, Janssen, Sanofi, Amgen, Gilead Sciences, BeiGene, AbbVie, Daiichi Sankyo/AstraZeneca, LEO Pharma, and Ipsen; having a family member employed by AstraZeneca; having travel, accommodations, or expenses paid by Roche; and receiving research funding from Roche, AstraZeneca, Bristol Myers Squibb, and MSD Avenir, outside of the current work.

Dr. Danchaivijitr reports receiving honoraria from Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Janssen, and Astellas Pharma; serving in a consulting or advisory role for Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Janssen, Astellas Pharma, and Eisai; participating in a speakers bureau for Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Janssen, Astellas, Amgen, BioPharma, and Eisai; and receiving research funding from Merck Sharp & Dohme, Roche, and Janssen, outside of the current work.

Dr. Alip reports serving in a consulting or advisory role for Boehringer Ingelheim, Cipla Malaysia, Eisai Malaysia, Ipsen, and Merck Sharp & Dohme; participating in a speakers bureau for Bristol Myers Squibb, AstraZeneca, and Ipsen; and receiving research funding from Janssen, Merck Sharp & Dohme, Novartis, and AstraZeneca, outside of the current work.

Dr. Mourão Dias reports serving in a consulting or advisory role for AstraZeneca and Merck Sharp & Dohme; participating in a speakers bureau for Amgen, AstraZeneca, Roche, Sanofi, Takeda, and Janssen; receiving research funding from AbbVie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Debiopharm Group, GlaxoSmithKline, Incyte, Ipsen, Janssen, Eli Lilly, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, and Xcovery; and having travel, accommodations, or expenses paid by Amgen, Boehringer Ingelheim, Janssen, and Sanofi, outside of the current work.

Dr. Lee reports receiving grants or contracts from Merck Serono; and receiving consulting fees from Merck Sharp & Dohme, Pfizer, Eli Lilly, Yuhan Corporation, AstraZeneca, and Bristol Myers Squibb, outside of the current work.

Dr. How reports having travel, accommodations, or expenses paid by Merck Sharp & Dohme; receiving honoraria from Roche, Merck Sharp & Dohme, and AstraZeneca; and receiving research funding from AstraZeneca, Merck Sharp & Dohme Oncology, Novartis, and Janssen Oncology, outside of the current work.

Dr. Chang reports receiving honoraria from F. Hoffmann-La Roche, Lilly Oncology, AstraZeneca, Novartis, Pfizer, Boehringer Ingelheim, Bristol Myers Squibb, and Merck Sharp & Dohme, outside of the current work.

Dr. Yang reports receiving honoraria from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche, and Takeda; serving in a consulting or advisory role for AbbVie, Amgen, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Clovis Oncology, Daiichi Sankyo, G1 Therapeutics, GlaxoSmithKline, Hansoh, Incyte, Janssen, Eli Lilly, Merck Serono, MSD Oncology, Novartis, Ono Pharmaceutical, Pfizer, Takeda, and Yuhan Corporation; and having travel, accommodations, or expenses paid by Pfizer, outside of the current work.

Dr. Besse reports participating in advisory board meetings (institution) with AbbVie, BioNTech SE, Beijing Avistone Biotechnology, Bristol Myers Squibb, CureVac AG, PharmaMar, Regeneron, and Sanofi-Aventis; serving in a consulting or advisory role for AbbVie, Bristol Myers Squibb, CureVac AG, Eli Lilly, Ellipses Pharma, F. Hoffman-La Roche, Foghorn Therapeutics, Genmab, Immunocore, Owkin, and Sanofi-Aventis; participating in a steering committee meeting (institution) with AstraZeneca, Amgen, BeiGene, CureVac AG, Genmab A/S, Janssen, Merck Sharp & Dohme, Ose Immunotherapeutics,

PharmaMar, Sanofi, and Takeda; and participating as a speaker (institution) for AbbVie, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme, Ose Immunotherapeutics, Sanofi-Aventis, and Servier, outside of the current work.

Dr. Thomas reports receiving grants or contracts from AstraZeneca, Bristol Myers Squibb, Merck, Roche, and Takeda; receiving consulting fees from Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Janssen, Eli Lilly, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi, and Takeda; receiving payment or honoraria from Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Daiichi Sankyo, GlaxoSmithKline, Janssen, Eli Lilly, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi, and Takeda; and receiving support for attending meetings and/or travel from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Janssen, Eli Lilly, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi, and Takeda, outside of the current work.

Dr. Shah, Dr. Baig, Dr. Curtin, Dr. Zhang, Dr. Xie, Dr. Sun, Dr. Sethi, Dr. Wang, Elizabeth Fennema, Dr. Daksh, Mariah Ennis, and Dr. Bauml report employment by and may hold stock in Johnson & Johnson.

Dr. Cho reports serving in a consulting or advisory role for AstraZeneca, Blueprint Medicines, Boehringer Ingelheim, BridgeBio, Bristol Myers Squibb, Cyrus Therapeutics, Guardant Health, Janssen, J INTS BIO, Kanaph Therapeutics, Eli Lilly, MedPacto, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche, Takeda, and Yuhan Corporation; serving in a leadership role for Interpark Bio and J INTS BIO; holding patents, royalties, or other intellectual property at Champions Oncology; having other relationships with DAAN Biotherapeutics; holding stock in Theravance, Gencurix, BridgeBio, Kanaph Therapeutics, Cyrus Therapeutics, and Interpark Bio; and receiving research funding from Novartis, Bayer, AstraZeneca, Mogam Biotechnology Research Institute, Dong-A ST, Champions Oncology, Janssen, and Yuhan Corporation, outside of the current work.

Dr. Kim, Dr. Ostapenko, Dr. Liu, Dr. Korbenfeld, Dr. Xiong, and Dr. Cheng report no disclosures.

Acknowledgments

The authors thank all the participants enrolled in this study and their families and caregivers. The authors also thank the physicians and nurses who cared for the participants, the staff at the clinical sites, and Roland E. Knoblauch and Melissa Martinez for their contributions to the study.

This study (ClinicalTrials.gov identifier: NCT04487080) was funded by Janssen Research & Development, LLC, a Johnson & Johnson company. Medical writing assistance was provided by David Le, PharmD, and Claire Brady, PharmD, of Lumanity Communications Inc., and funded by Johnson & Johnson.

Data Sharing Statement

The data-sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale University Open Data Access (YODA) project site at http://yoda.yale.edu.

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.2025.06.030.

References

1. Gazdar AF. Activating and resistance mutations of *EGFR* in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene*. 2009;28(suppl 1):S24–S31.
2. Vyse S, Huang PH. Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer. *Signal Transduct Target Ther*. 2019;4:5.
3. Cheng Z, Cui H, Wang Y, et al. The advance of the third-generation EGFR-TKI in the treatment of non-small cell lung cancer (Review). *Oncol Rep*. 2024;51:16.
4. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
5. Cho BC, Ahn MJ, Kang JH, et al. Lazertinib versus gefitinib as first-line treatment in patients with *EGFR*-mutated advanced non-small-cell lung cancer: results from LASER301. *J Clin Oncol*. 2023;41:4208–4217.
6. Ahn MJ, Han JY, Lee KH, et al. Lazertinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: results from the dose escalation and dose expansion parts of a first-in-human, open-label, multicentre, phase 1-2 study. *Lancet Oncol*. 2019;20:1681–1690.
7. Cho BC, Han JY, Kim SW, et al. A phase 1/2 study of lazertinib 240 mg in patients with advanced *EGFR* T790M-positive NSCLC after previous EGFR tyrosine kinase inhibitors. *J Thorac Oncol*. 2022;17:558–567.
8. Heppner DE, Wittlinger F, Beyett TS, et al. Structural basis for inhibition of mutant EGFR with lazertinib (YH25448). *ACS Med Chem Lett*. 2022;13:1856–1863.
9. Yun J, Hong MH, Kim SY, et al. YH25448, an irreversible EGFR-TKI with potent intracranial activity in EGFR mutant non-small cell lung cancer. *Clin Cancer Res*. 2019;25:2575–2587.
10. Cho BC, Lu S, Felip E, et al. Amivantamab plus lazertinib in previously untreated *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2024;391:1486–1498.

11. Yang JC-H, Kim YJ, Lee S-H, et al. Amivantamab plus lazertinib vs osimertinib in first-line (1L) *EGFR*-mutant (EGFRm) advanced NSCLC: final overall survival (OS) from the phase III MARIPOSA study. Presented at the European Lung Cancer Congress (ELCC); March 26-29, 2025; Paris, France. 2025.
12. Janssen Biotech, Inc. RYBREVANT (amivantamab-vmjw) injection, for intravenous use [prescribing information]. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RYBREVANT-pi.pdf. Accessed July 22, 2025.
13. Johnson & Johnson. European Commission approves RYBREVANT®(amivantamab) in combination with LAZCLUZE®(lazertinib) for the first-line treatment of patients with EGFR-mutated advanced non-small cell lung cancer. https://www.jnj.com/media-center/press-releases/european-commission-approves-rybrevant-amivantamab-in-combination-with-lazcluze-lazertinib-for-the-first-line-treatment-of-patients-with-egfr-mutated-advanced-non-small-cell-lung-cancer. Accessed July 22, 2025.
14. Watson AS, Patil T, Schenk EL, Camidge DR. Early onset venous and arterial thrombosis when combining osimertinib and amivantamab in NSCLC: instructive cases and literature review. *Case Rep*. 2025;17:100348.
15. Bak M, Park H, Lee SH, et al. The risk and reversibility of osimertinib-related cardiotoxicity in a real-world population. *J Thorac Oncol*. 2025;20:167–176.
16. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2020;382:41–50.
17. Girard N, Ohe Y, Kim TM, et al. Mortality among EGFR-mutated advanced NSCLC patients after frontline osimertinib treatment: a real-world, US attrition analysis. *J Thorac Oncol*. 2023;18:S51–S52.
18. Nieva J, Reckamp KL, Potter D, Taylor A, Sun P. Retrospective analysis of real-world management of *EGFR*-mutated advanced NSCLC, after first-line EGFR-TKI treatment: US treatment patterns, attrition, and survival data. *Drugs Real World Outcomes*. 2022;9:333–345.
19. Lee JY, Mai V, Garcia M, et al. EP08.02-082 Treatment patterns and outcomes of first-line osimertinib-treated advanced EGFR mutated NSCLC patients: a real-world study. *J Thorac Oncol*. 2022;17:S440.
20. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in *EGFR*-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121:725–737.
21. Yu HA, Kerr K, Rolfo CD, et al. Detection of *MET* amplification (*MET* amp) in patients with *EGFR* mutant (m) NSCLC after first-line (1L) osimertinib. *J Clin Oncol*. 2023;41(16_suppl):9074.
22. Ramalingam SS, Cheng Y, Zhou C, et al. LBA750 - Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study. *Ann Oncol*. 2018;29(suppl 8):VIII740.
23. Besse B, Lee SH, Lu S, et al. LBA55 Mechanisms of acquired resistance to first-line amivantamab plus lazertinib versus osimertinib in patients with EGFR-mutant advanced non-small cell lung cancer: an early analysis from the phase III MARIPOSA study. *Ann Oncol*. 2024;35:S1245–S1246.
24. Chmielecki J, Gray JE, Cheng Y, et al. Candidate mechanisms of acquired resistance to first-line osimertinib in EGFR-mutated advanced non-small cell lung cancer. *Nat Commun*. 2023;14:1070.