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Research Paper

Amivantamab plus lazertinib versus osimertinib as first-line treatment in *EGFR*-mutated advanced non-small cell lung cancer: MARIPOSA Asian subset

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ABSTRACT

Introduction: The incidence of epidermal growth factor receptor (*EGFR*) mutations is higher among Asian patients with advanced non-small cell lung cancer than the general advanced non-small cell lung cancer population. We evaluated the efficacy and safety of amivantamab in combination with lazertinib versus osimertinib in Asian participants from the phase 3 MARIPOSA study who had treatment-naïve advanced non-small cell lung cancer with common *EGFR* mutations.

Methods: Participants were randomized 2:2:1 to receive amivantamab-lazertinib, osimertinib alone, or lazertinib alone. The primary endpoint was progression-free survival based on blinded independent central review per RECIST v1.1. Secondary endpoints included overall survival, objective response rate, duration of response, and safety. Exploratory endpoints included extracranial progression-free survival and post-progression outcomes.

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Results: Of 1074 randomized participants, 629 were Asian, with 250 and 251 randomized to the amivantamab-lazertinib and osimertinib arms, respectively. Among Asian participants, at a median follow-up of 22.5 months, amivantamab-lazertinib showed a 35 % reduction in the risk of disease progression or death versus osimertinib (hazard ratio, 0.65; $P < 0.001$). Consistent with the overall population, median progression-free survival was 27.5 and 18.3 months in the amivantamab-lazertinib and osimertinib arms, respectively. The objective response rate was 88 % for amivantamab-lazertinib versus 85 % for osimertinib. The median duration of response among confirmed responders improved by 8.6 months for amivantamab-lazertinib versus osimertinib. Favorable trends were also seen for overall survival, extracranial progression-free survival, and post-progression outcomes for amivantamab-lazertinib over osimertinib. Adverse events in Asian participants were similar to those in the overall population.
Conclusions: Amivantamab-lazertinib demonstrated superior progression-free survival versus osimertinib in Asian participants, with a tolerable safety profile. These results were consistent with those in the overall population.

Nomenclature

AE	adverse event
BICR	blinded independent central review
CI	confidence interval
CNS	central nervous system
DoR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
Ex19del	exon 19 deletion
HR	hazard ratio
MRI	magnetic resonance imaging
NE	not estimable
NSCLC	non-small cell lung cancer
OR	odds ratio
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PFS2	progression-free survival after first subsequent therapy
RECIST	Response Evaluation Criteria in Solid Tumors
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTD	time to treatment discontinuation
TTST	time to subsequent therapy
VTE	venous thromboembolism

1. Introduction

Lung cancer is the most prevalent type of cancer in Asia, comprising 15.9 % of all new cancer cases in 2022 [1]. It is particularly prevalent in Eastern Asia, including China, Japan, Mongolia, North Korea, and South Korea, where it accounted for 20.3 % of all new cancer cases in 2022 [2]. Non-small cell lung cancer (NSCLC) accounts for 80 % of all lung cancer cases [3]. Activating mutations in the epidermal growth factor receptor (*EGFR*) gene are especially prevalent in Asian patients and present in 38 % to 47 % of patients of Asian race with NSCLC compared with approximately 17 % of non-Asian patients [4,5]. Of all *EGFR* mutations seen in NSCLC, 85 % to 90 % are exon 19 deletions (Ex19del) or exon 21 L858R substitution mutations, also known as common *EGFR* mutations [6,7].

Multiple targeted treatment approaches, including EGFR tyrosine kinase inhibitors (TKIs), are available for Asian patients with *EGFR*-mutated NSCLC. Although third-generation EGFR TKIs such as osimertinib have shown improved outcomes over first- and second-generation EGFR TKIs [8,9], first-line treatment with third-generation TKIs results in a median overall survival (OS) of approximately 3 years and an estimated real-world 5-year survival rate of < 20 % [9–11]. Furthermore, approximately 25 % to 40 % of patients treated with third-generation EGFR TKIs do not receive second-line therapy [12–14]. Finally, nearly all patients eventually develop resistance to third-generation EGFR TKIs through diverse and polyclonal mechanisms, which may explain the poor real-world outcomes observed [15–17]. Therefore, it is important to administer the most efficacious therapy first.

In an Asian subpopulation, osimertinib demonstrated an improved PFS compared with first-generation EGFR TKIs, with a hazard ratio (HR) of 0.55 (95 % confidence interval [CI]: 0.42–0.72) [8]. However, osimertinib did not demonstrate an OS advantage in the Asian subpopulation (HR, 1.00; 95 % CI: 0.75–1.32) while a strong benefit was observed among the non-Asian subpopulation (HR, 0.54; 95 % CI: 0.38–0.77) [8,9]. Osimertinib in combination with chemotherapy is approved in the United States for patients with treatment-naïve NSCLC with common *EGFR* mutations based on results from the phase 3 FLAURA-2 study [18,19]. However, this treatment combination did not demonstrate an OS benefit in non-Chinese Asian participants, with an HR of 1.04 (95 % CI: 0.70–1.54), while Chinese-Asian and non-Asian participants demonstrated an HR of 0.49 (95 % CI: 0.27–0.91) and 0.64 (95 % CI: 0.41–0.99), respectively [10].

Amivantamab, an EGFR-MET bispecific antibody, has a unique multitargeted mechanism of action, including ligand blocking, receptor degradation, and engagement of immune effector cells (monocytes, macrophages, natural killer cells) via its optimized Fc domain [20–23]. Amivantamab, alone and in combination with chemotherapy, has been studied and shown as beneficial compared with the current standards of care among patients with common and other *EGFR* mutations, including Asian patients [24–28]. Amivantamab in combination with chemotherapy is currently approved for use in Japan, Taiwan, Europe, and the United States for patients with treatment-naïve NSCLC with *EGFR* exon 20 insertion mutations [24,29–32]. Additionally, it is approved in combination with chemotherapy in Europe and the United States for patients with common *EGFR* mutations after disease progression on an EGFR TKI [24,32]. Amivantamab is also approved as a monotherapy for patients with *EGFR* exon 20 insertion mutations whose disease has progressed on platinum-based chemotherapy [24,32].

In the phase 3 MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) study, at a median follow-up of 22.0 months, amivantamab combined with lazertinib, a highly selective central nervous system (CNS)–penetrant third-generation EGFR TKI, demonstrated superior progression-free survival (PFS; HR, 0.70; $P < 0.001$) compared with osimertinib in participants with treatment-naïve, *EGFR*-mutated advanced NSCLC. The PFS benefit persisted across key predefined subgroups, including participants with or without a history of brain metastases [33]. With longer follow-up (median follow-up of 31.1 months), median OS in the amivantamab-lazertinib arm was not estimable (NE) compared with 37.3 months for osimertinib (HR, 0.77; 95 % CI: 0.61–0.96; $P = 0.019$) [34]. Based on

these results, amivantamab-lazertinib was recently approved in the United States and Europe as a first-line treatment for patients with advanced NSCLC harboring common *EGFR* mutations [24,35].

The most common resistance mechanisms to third-generation EGFR TKIs are secondary *EGFR* pathway alterations and *MET* pathway activation, but around 50 % of patients do not have an identified resistance mechanism, making subsequent treatment selection challenging [15]. In MARIPOSA, amivantamab-lazertinib meaningfully reduced the incidence of acquired *EGFR* resistance (7.9 % vs 0.9 %; $P = 0.014$) and *MET* amplifications compared with osimertinib (13.6 % vs 4.4 %; $P = 0.017$) [36]. Based on these results, amivantamab can potentially address the unmet needs among patients with NSCLC harboring common *EGFR* mutations, including Asian patients, when used in combination with lazertinib, by proactively targeting mechanisms of resistance before they emerge.

Here, we report the safety and efficacy of amivantamab-lazertinib among Asian participants enrolled in the MARIPOSA study.

2. Materials and methods

2.1. Participants

MARIPOSA enrolled participants 18 years of age or older with treatment-naïve locally advanced or metastatic NSCLC harboring common *EGFR* mutations (Ex19del or L858R), with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Details of the study design and methodology have been previously described [33]. This analysis includes participants of self-reported Asian race enrolled in Australia, Brazil, China, France, Germany, India, Japan, Malaysia, Russia, South Korea, Spain, Taiwan, Thailand, the United States, and the United Kingdom. Participants were included in the analysis if their self-reported race was "Asian" or "mixed" with any Asian component.

2.2. Study design and treatment

Participants were randomly assigned in a 2:2:1 ratio to receive amivantamab-lazertinib, osimertinib monotherapy, or lazertinib monotherapy. Randomization for the overall population enrolled in the study was stratified by *EGFR* mutation type (Ex19del vs L858R), race (Asian vs non-Asian), and history of brain metastases (present vs absent).

Intravenous amivantamab was administered weekly at a dose of 1050 mg (1400 mg for body weight $\geq$ 80 kg) for the first 4 weeks (Cycle 1), with the first infusion split over 2 days (350 mg given on Cycle 1 Day 1, with remainder on Cycle 1 Day 2). Starting at Cycle 2, the same amivantamab dose was administered every 2 weeks. Osimertinib (80 mg) and lazertinib (240 mg) were dosed orally daily. Prophylactic anticoagulation to prevent venous thromboembolism (VTE) was recommended per local guidelines for the first 4 months of amivantamab-lazertinib but not required. This recommendation was added as an amendment to the protocol after enrollment to the study had been completed, and very few participants in the overall population (5 %) received anticoagulants at baseline [33].

2.3. Study oversight

The study was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Council for Harmonisation), applicable regulatory requirements, and policy on bioethics and human biologic samples of the study sponsor, Johnson & Johnson. The study was designed by representatives of the sponsor, who were responsible for data collection, analysis, and interpretation of study data in collaboration with the authors. Written informed consent was provided by all participants. The study protocol was approved by an independent ethics committee or institutional review board.

2.4. Endpoints and assessments

The primary endpoint was PFS of amivantamab-lazertinib versus osimertinib as determined by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. A prespecified subgroup analysis was conducted to assess internal consistency and homogeneity of the treatment effect. Serial CNS assessments were conducted in all participants by means of a magnetic resonance imaging (MRI) scan of the head, which is not frequently done in clinical trials. To better assess the efficacy of amivantamab-lazertinib among participants without CNS-only progressive disease, a sensitivity analysis was performed to evaluate extracranial PFS, which was defined as time from randomization to disease progression detected by extracranial scans or death; if the first progression was only in the CNS, the participant was censored at the time of progression.

OS was a key secondary endpoint. Other secondary endpoints included PFS after first subsequent therapy (PFS2), defined as the time from randomization to second objective disease progression after first subsequent therapy, objective response rate (ORR), duration of response (DoR), and safety. Time to treatment discontinuation (TTD) and time to subsequent therapy (TTST) were assessed as exploratory endpoints.

Disease assessments were performed at baseline, then every 8 weeks ($\pm$1 week) for the first 30 months, and every 12 weeks ($\pm$1 week) thereafter until disease progression using computed tomography and MRI confirmed by BICR. Imaging of the head was done at baseline, with subsequent imaging (until disease progression) occurring every 8 weeks ($\pm$1 week) for the first 30 months and then every 12 weeks ($\pm$1 week) in participants with a history of brain metastases or every 24 weeks ($\pm$1 week) in participants without a history of brain metastases.

2.5. Statistical methods

Asian participants were a subgroup of the overall population for which there was no formal sample size or power calculation. All efficacy outcomes were analyzed in Asian participants from the full analysis set (all randomized participants; intent-to-treat). All safety outcomes were analyzed in Asian participants from the safety analysis set (all participants who received $\geq$1 dose of study treatment).

PFS was analyzed by the Kaplan–Meier method by treatment arm, with medians, 95 % CIs, and number of events summarized. Significance was assessed using a log-rank test stratified by mutation type and history of brain metastases.

For the overall population, a hierarchical testing approach was used for OS. This exploratory subgroup analysis was not part of the hierarchical testing approach, and therefore the *P*-values for all endpoints are nominal. HRs and their corresponding 95 % CIs were calculated from a stratified Cox model.

All results reported are based on the primary analysis, which was conducted on data collected by the cutoff date of August 11, 2023. This analysis only includes the comparison between the amivantamab-lazertinib and osimertinib arms.

3. Results

3.1. Participants

Of the 1074 participants enrolled in MARIPOSA between November 2020 and May 2022, 629 were of Asian race (250 assigned to amivantamab-lazertinib, 251 to osimertinib, and 128 to lazertinib). A total of 625 Asian participants received $\geq$1 dose of the assigned treatment (**Fig. S1**). Baseline demographic and disease characteristics were generally balanced between treatment arms (Table 1) and aligned with those of the overall population [33]. The majority of participants were female (61 % in the amivantamab-lazertinib arm and 57 % in the osimertinib arm) and had no history of tobacco use (72 % in both arms). Most participants in each treatment arm harbored Ex19del (55 %).

Table 1
Demographic and Baseline Disease Characteristics Among Asian Participants.

Characteristic	Amivantamab-lazertinib (n = 250)	Osimertinib (n = 251)
Age		
Median age (range), years	63 (35–85)	63 (28–88)
Category, n (%)		
<65 years	143 (57)	140 (56)
≥65 to <75 years	81 (32)	87 (35)
≥75 years	26 (10)	24 (10)
Sex, n (%)		
Female	152 (61)	143 (57)
Male	98 (39)	108 (43)
Region of enrollment, n (%)		
North America	2 (0.8)	2 (0.8)
South America	0	1 (0.4)
Europe	1 (0.4)	4 (2)
Asia	245 (98)	242 (96)
Oceania	2 (0.8)	2 (0.8)
Body weight		
Median, kg (range)	59.1 (32–90)	58.0 (35–97)
Category, n (%)		
<80 kg	236 (94)	238 (95)
≥80 kg	14 (6)	13 (5)
ECOG PS, n (%)		
0	69 (28)	84 (33)
1	181 (72)	167 (67)
EGFR mutation type, n (%)[a]		
Ex19del	138 (55)	139 (55)
L858R	113 (45)	112 (45)
History of tobacco use, n (%)		
No	180 (72)	181 (72)
Yes	70 (28)	70 (28)
History of brain metastases, n (%)	110 (44)	108 (43)
Histologic type, n (%)		
Adenocarcinoma histology	244 (98)	239 (95)
Large cell carcinoma	1 (0.4)	0
Squamous cell carcinoma	4 (2)	4 (2)
Other[b]	1 (0.4)	8 (3)
Time from initial diagnosis, median (range), mo	1.2 (0.2–208)	1.2 (0.3–135.2)
Time from metastatic disease diagnosis, median (range), mo	1.1 (0.2–24.1)	1.1 (0.1–9.1)

Note: percentages may not sum to 100 due to rounding.
[a] One participant in the amivantamab-lazertinib group had both Ex19del and L858R.
[b] Other histologic types included adenocarcinoma and squamous cell carcinoma, lepidic adenocarcinoma, non-small cell carcinoma, pleomorphic carcinoma, and unknown.

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion.

Baseline CNS metastases were observed in 44 % of participants in the amivantamab-lazertinib arm and 43 % in the osimertinib arm.

At a median follow-up of 22.5 months, the median (range) duration of study treatment for the amivantamab-lazertinib and osimertinib arms was 19.8 months (0.2–31.4) and 18.7 months (0.2–31.9), respectively. At data cutoff, 139 (56 %) participants in the amivantamab-lazertinib arm and 127 (51 %) participants in the osimertinib arm were still receiving their assigned treatment. The most common reasons for treatment discontinuation were progressive disease (50 [20 %] participants for amivantamab-lazertinib; 88 [35 %] participants for osimertinib) and adverse events (AEs; 47 [19 %] participants for amivantamab-lazertinib; 25 [10 %] participants for osimertinib).

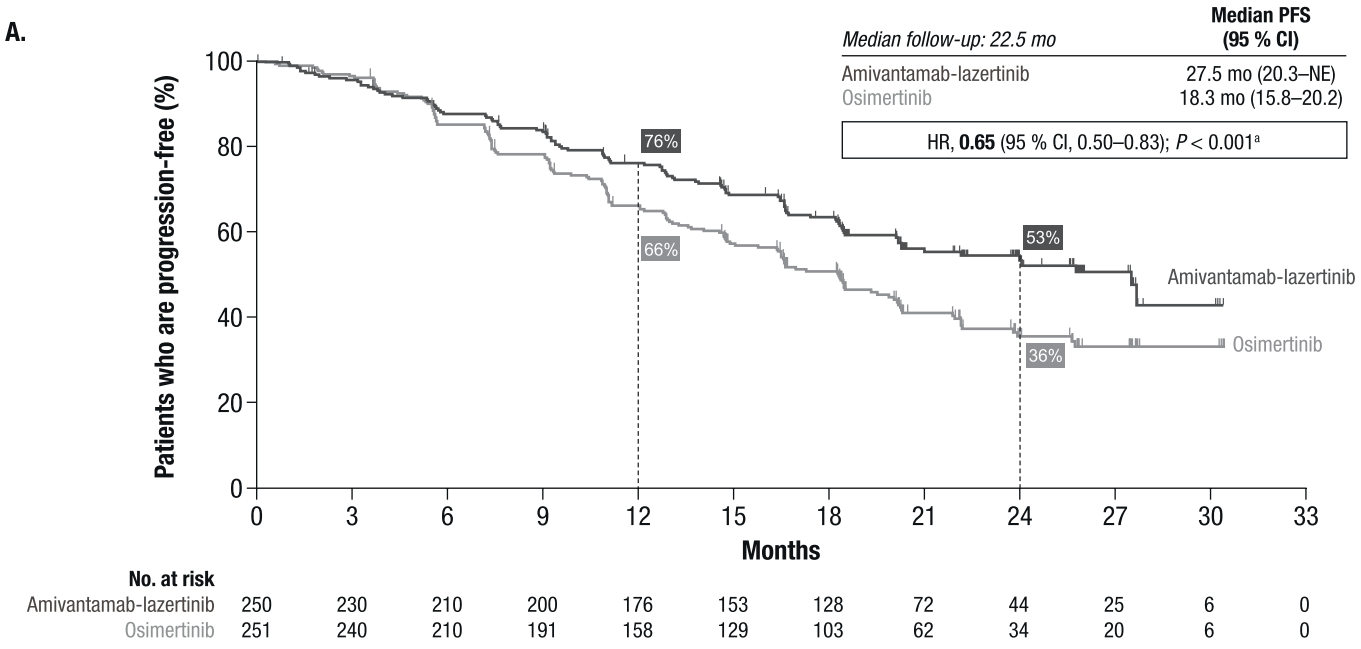
3.2. Efficacy

All Asian participants in the amivantamab-lazertinib (n = 250) and osimertinib (n = 251) arms were included in the efficacy analysis. Median PFS determined by BICR was significantly longer in the amivantamab-lazertinib arm at 27.5 months (95 % CI: 20.3–NE) versus 18.3 months (95 % CI: 15.8–20.2) in the osimertinib arm (HR, 0.65; 95 % CI: 0.50–0.83; nominal $P < 0.001$; Fig. 1**A**). At 18 months, 64 % (95 % CI: 57–69) of participants in the amivantamab-lazertinib arm and 51 % (95 % CI: 44–57) of participants in the osimertinib arm were progression-free; corresponding values at 24 months were 53 % (95 % CI: 46–60) and 36 % (95 % CI: 29–43), respectively (Table 2).

PFS values among predefined subgroups consistently favored amivantamab-lazertinib over osimertinib (Fig. 1**B**). Among participants with CNS metastases at baseline, median PFS was 18.3 (95 % CI: 16.5–20.3) months in the amivantamab-lazertinib arm versus 14.7 (95 % CI: 12.2–16.6) months in the osimertinib arm (HR, 0.72; 95 % CI: 0.51–1.02; nominal $P = 0.062$; **Fig. S2**). Among participants harboring Ex19del mutations, median PFS was NE (95 % CI: 25.8–NE) in the amivantamab-lazertinib arm versus 20.0 (95 % CI: 16.6–25.6) months in the osimertinib arm (HR, 0.61; 95 % CI: 0.42–0.88; **Fig. S3A**). Among participants with L858R substitutions, median PFS was 18.5 (95 % CI: 16.7–NE) months in the amivantamab-lazertinib arm versus 16.4 (95 % CI: 11.2–18.4) months in the osimertinib arm (HR, 0.71; 95 % CI: 0.50–1.00; **Fig. S3B**).

Extracranial PFS was 27.7 (95 % CI: 24.1–NE) months in the amivantamab-lazertinib arm versus 19.3 (95 % CI: 16.6–22.1) months in the osimertinib arm (HR, 0.62; 95 % CI: 0.47–0.81; nominal $P < 0.001$).

ORR was 88 % in the amivantamab-lazertinib arm and 85 % in the osimertinib arm (odds ratio, 1.29; 95 % CI: 0.76–2.17; Table 2). Median DoR among confirmed responders improved in the amivantamab-lazertinib arm by 8.6 months compared with the osimertinib arm (26.1 [95 % CI: 20.1–NE] vs 17.5 [95 % CI: 14.8–20.4] months; Fig. 2**A**).



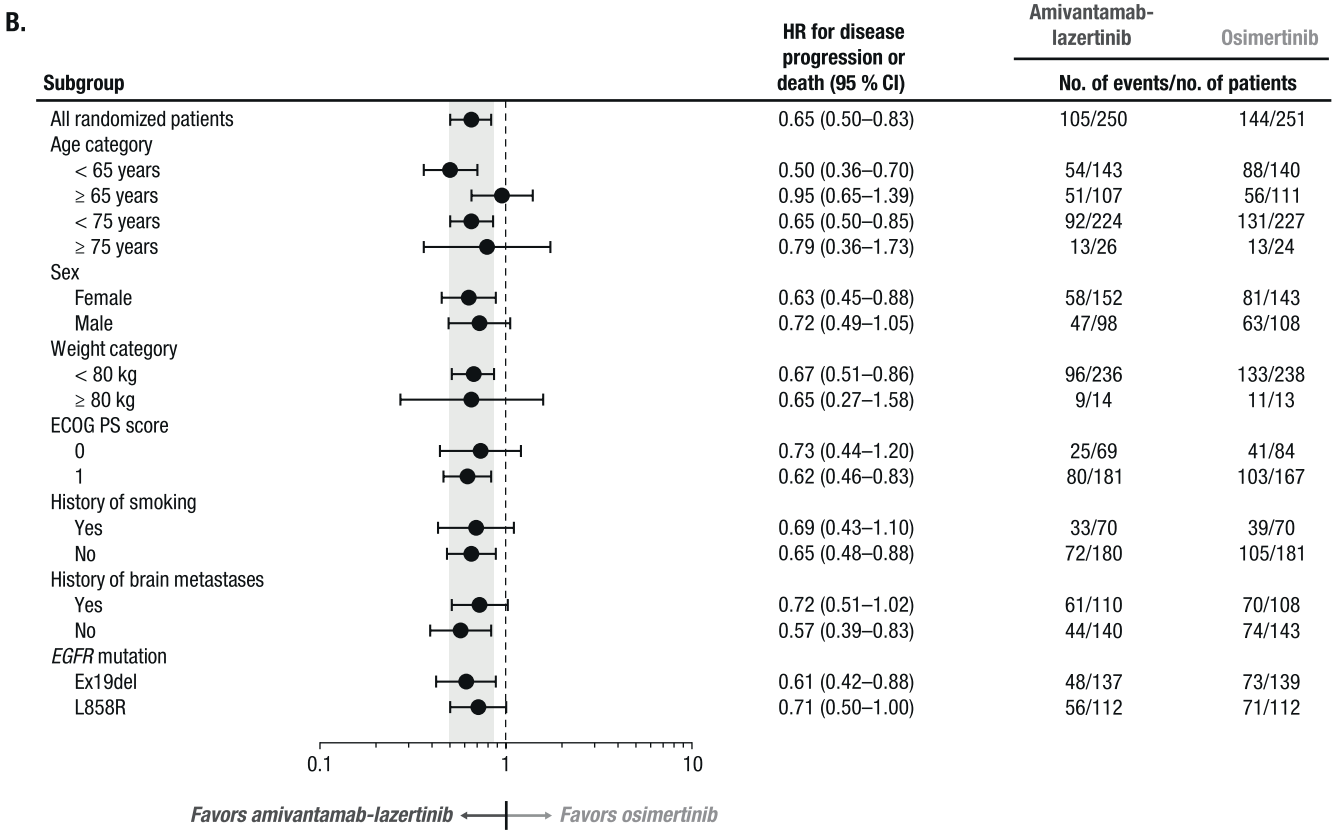


Fig. 1. PFS by BICR (A) Among Asian Participants and (B) Among Predefined Subgroups of Asian Participants.
Note: Gray box indicates 95% CI of HR for all randomized participants. HR for the analysis of all randomized participants is from a proportional hazards model stratified by mutation type and history of brain metastasis. HR for the analysis of subgroups is from an unstratified proportional hazards model.
[a]Nominal *P*-value; endpoint is not part of hierarchical hypothesis testing.
BICR, blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

Table 2
Key Efficacy Endpoints.

Endpoints	Amivantamab-lazertinib (n = 250)	Osimertinib (n = 251)	Treatment effect (95 % CI)	*P*-value
PFS				
Median (95 % CI), mo	27.5 (20.3–NE)	18.3 (15.8–20.2)	HR, 0.65 (0.50–0.83)	< 0.001[a]
Participants (95 % CI), %				
At 12 months	76 (70–81)	66 (60–72)		
At 18 months	64 (57–69)	51 (44–57)		
At 24 months	53 (46–60)	36 (29–43)		
OS				
Median (95 % CI), mo	NE (NE–NE)	NE (NE–NE)	HR, 0.84 (0.58–1.23)	0.38[a]
Participants (95 % CI), %				
At 12 months	93 (89–95)	90 (85–93)		
At 18 months	85 (79–89)	83 (77–87)		
At 24 months	78 (72–83)	75 (69–81)		
ORR[b]				
Participants (95 % CI), %	88 (84–92)	85 (80–90)	OR, 1.29 (0.76–2.17)	0.35
Best response, n (%)				
CR	19 (8)	10 (4)		
PR	200 (81)	202 (81)		
SD	15 (6)	25 (10)		
PD	3 (1)	4 (2)		
Not evaluable	11 (4)	7 (3)		
DoR[c]				
Median (95 % CI), mo	26.1 (20.1–NE)	17.5 (14.8–20.4)		

[a] Nominal *P*-value; endpoint is not part of hierarchical hypothesis testing.
[b] Number of participants with measurable disease at baseline by BICR was 248 for both treatment groups; includes all responders.
[c] Among confirmed responders.
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; NE, not estimable; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Median OS was NE for both arms at the time of interim analysis but showed a favorable trend for amivantamab-lazertinib (HR, 0.84; 95 % CI: 0.58–1.23; nominal $P = 0.38$; Fig. 2**B**).

Favorable trends were also seen for post-progression outcomes, including PFS2, TTD, and TTST. Median PFS2 was NE for both arms at the time of the analysis but favored amivantamab-lazertinib (HR, 0.78; 95 % CI: 0.54–1.11; nominal $P = 0.17$; Fig. 2**C**). In total, 67 participants in the amivantamab-lazertinib arm and 101 participants in the osimertinib arm discontinued study treatment due to investigator-assessed disease progression. Median TTD was 27.7 (95 % CI: 23.1–NE) months in the amivantamab-lazertinib arm versus 23.1 (95 % CI: 20.3–NE) months in the osimertinib arm (HR, 0.84; 95 % CI: 0.65–1.09; nominal $P = 0.18$; **Fig. S4**). Of those participants who discontinued treatment, 66 % (44/67) in the amivantamab-lazertinib arm and 72 % (73/101) in the osimertinib arm received subsequent therapy. The most common subsequent therapy category in the amivantamab-lazertinib and osimertinib arms was chemotherapy (**Fig. S5**). TTST was NE (95 % CI: 28.1–NE) in the amivantamab-lazertinib arm versus 25.4 (95 % CI: 23.0–NE) months in the osimertinib arm (HR, 0.78; 95 % CI: 0.59–1.03; nominal $P = 0.08$; **Fig. S6**).

3.3. Safety

Overall, rates of AEs in the Asian subpopulation were comparable to the overall rates observed in MARIPOSA [33]. Most participants in both arms of the study had ≥1 AE (Table 3). The most common grade ≥3 AEs in the amivantamab-lazertinib arm included rash (reported by 17 % of participants in the amivantamab-lazertinib arm and 1 % in the osimertinib arm), paronychia (8 % and 1 %), and dermatitis acneiform (8 % and 0 %). Serious AEs were reported in 47 % and 32 % of participants in the amivantamab-lazertinib and osimertinib arms, respectively.

VTE was reported in 31 % (n = 77) of participants in the amivantamab-lazertinib arm compared with 6 % (n = 14) of participants in the osimertinib arm, with most events occurring within the first 4 months of treatment. Among participants with VTE, 76 (99 %) were not on anticoagulants at the time of the event. No grade 4 or 5 VTE was reported. Interstitial lung disease rates were low and similar in the amivantamab-lazertinib and osimertinib arms (4 % vs 3 %), consistent with the rates observed in the overall population (3 % in each arm).

Discontinuations of any drug due to an AE occurred in 29 % of participants in the amivantamab-lazertinib arm and 12 % in the osimertinib arm (Table 3). Dose reductions due to AEs occurred in 58 % of participants in the amivantamab-lazertinib arm and 6 % in the osimertinib arm. Dose interruptions due to AEs occurred in 84 % of participants in the amivantamab-lazertinib arm and 39 % in the osimertinib arm.

4. Discussion

Lung cancer poses a substantial burden in Asia, particularly in the Eastern part of the continent [1,2]. Despite existing therapies for NSCLC harboring common *EGFR* mutations, there are substantial unmet needs for Asian patients [8,9].

In the primary analysis of the phase 3 MARIPOSA study, first-line treatment with amivantamab-lazertinib significantly prolonged PFS versus osimertinib monotherapy in participants with common *EGFR* mutations (HR, 0.70; $P < 0.001$). In MARIPOSA, 58 % of participants in the amivantamab-lazertinib and osimertinib arms self-reported as Asian; of those, approximately 97 % were from Asian countries. As reported here, efficacy and safety results for participants of Asian race were consistent with those of the overall population [33]. A significantly higher median PFS was observed in the amivantamab-lazertinib arm compared with the osimertinib arm (HR, 0.65; nominal $P < 0.001$). Furthermore, a consistent PFS benefit was observed for the amivantamab-lazertinib arm across predefined subgroups, including those with and without brain metastases.

It should be noted that due to the high incidence of brain metastases in patients with *EGFR*-mutated NSCLC, MARIPOSA conducted serial brain MRIs on all participants, which is not routinely done in trials for this patient population. These scans may detect CNS progression earlier than what has been reported from trials that monitored CNS disease less frequently or did not have any mandatory monitoring. Thus, an

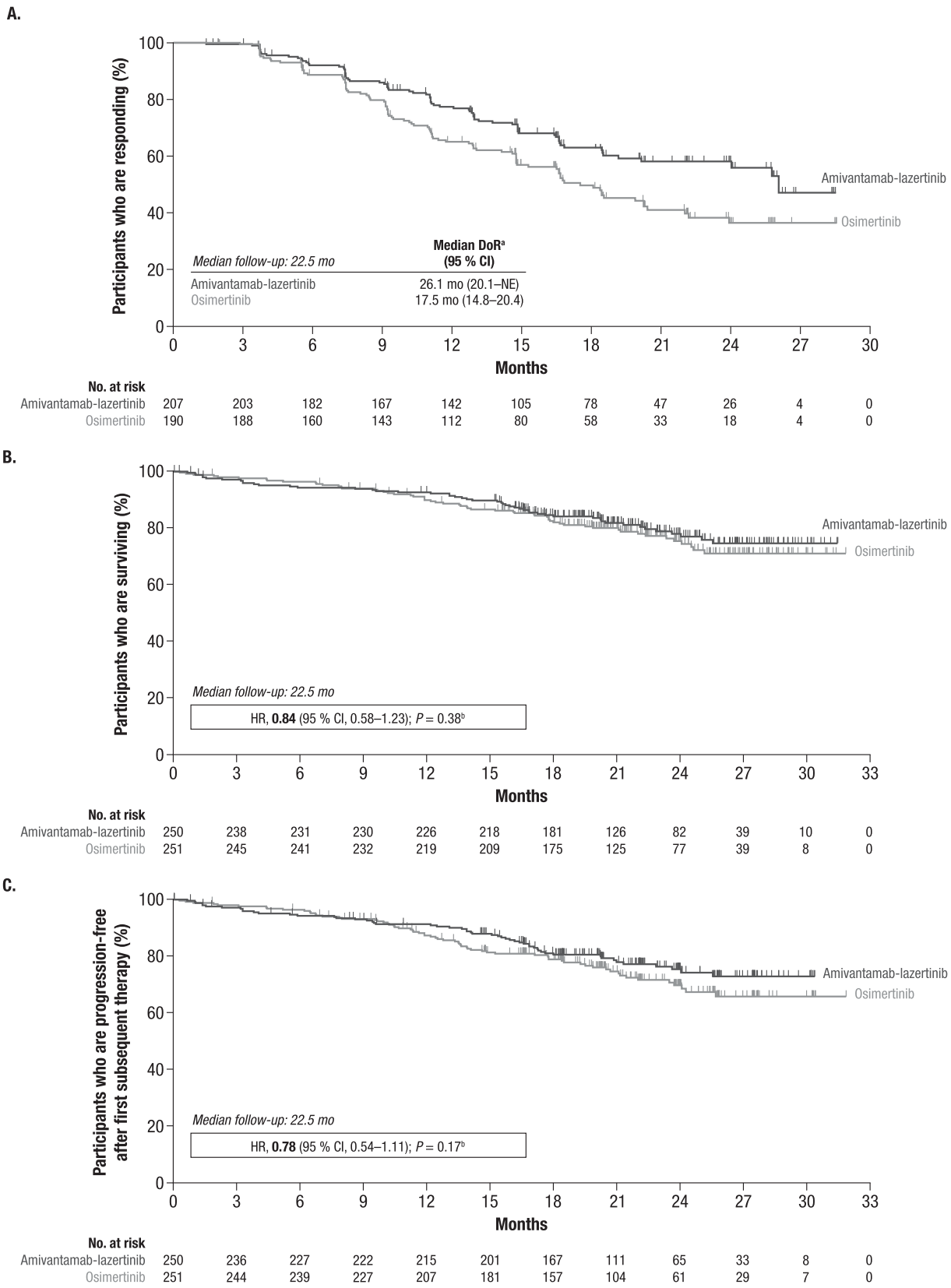


Fig. 2. (A) DoR by BICR (B) Interim OS and (C) PFS2 Among Asian Participants.
Note: PFS2 is defined as the time from randomization until the time of second objective disease progression (based on investigator assessment) or death, whichever comes first, after the initiation of the first subsequent systemic anticancer therapy.
[a]Among confirmed responders. [b]Nominal *P*-value; endpoint is not part of hierarchical hypothesis testing.
BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS2, progression-free survival after first subsequent therapy.

Table 3
Safety Profile Among Asian Participants.

TEAEs, n (%)	Amivantamab-lazertinib (n = 248)		Osimertinib (n = 250)	
Any AEs	248 (100)		247 (99)	
Grade ≥ 3 AEs	176 (71)		102 (41)	
Serious AEs	117 (47)		80 (32)	
AEs leading to death	17 (7)		12 (5)	
Any AE leading to:				
Interruption of any agent[a]	208 (84)		98 (39)	
Reduction of any agent	145 (58)		14 (6)	
Discontinuation of any agent	73 (29)[b]		30 (12)	
Most common TEAEs (≥ 15 %) by preferred term	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Paronychia	182 (73)	21 (8)	79 (32)	2 (1)
Rash	158 (64)	41 (17)	82 (33)	2 (1)
Infusion-related reaction	150 (60)	7 (3)	0	0
Hypoalbuminemia	140 (56)	17 (7)	19 (8)	0
Alanine aminotransferase increased	89 (36)	10 (4)	40 (16)	4 (2)
Constipation	85 (34)	0	34 (14)	0
Stomatitis	84 (34)	3 (1)	79 (32)	1 (0.4)
Peripheral edema	83 (33)	3 (1)	10 (4)	0
Aspartate aminotransferase increased	77 (31)	8 (3)	43 (17)	3 (1)
Dermatitis acneiform	73 (29)	21 (8)	36 (14)	0
Decreased appetite	70 (28)	4 (2)	44 (18)	2 (1)
COVID-19	66 (27)	4 (2)	62 (25)	5 (2)
Diarrhea	65 (26)	4 (2)	105 (42)	1 (0.4)
Anemia	57 (23)	9 (4)	49 (20)	5 (2)
Pruritus	51 (21)	1 (0.4)	55 (22)	0
Nausea	50 (20)	3 (1)	23 (9)	0
Hypokalemia	49 (20)	11 (4)	25 (10)	2 (1)
Hypocalcemia	47 (19)	7 (3)	22 (9)	0
Dry skin	46 (19)	1 (0.4)	36 (14)	1 (0.4)
Thrombocytopenia	43 (17)	1 (0.4)	48 (19)	5 (2)
Cough	40 (16)	0	47 (19)	0
Fatigue	39 (16)	3 (1)	17 (7)	1 (0.4)
Leukopenia	22 (9)	1 (0.4)	51 (20)	0
Neutropenia	16 (6)	4 (2)	41 (16)	2 (1)

Note: Data are reported for the safety population, which included all randomized participants who received ≥ 1 dose of any study treatment.
[a] Excludes infusion-related reactions.
[b] 72 (29 %) participants discontinued amivantamab and 47 (19 %) participants discontinued lazertinib.
AE, adverse event; TEAE, treatment-emergent adverse event.

extracranial PFS analysis was performed, which censored participants with CNS-only progressive disease as a site of first progression, to allow for a more accurate comparison with other trials. In this analysis, amivantamab-lazertinib substantially prolonged extracranial PFS compared with osimertinib (27.7 months vs 19.3 months; HR, 0.62; nominal $P < 0.001$).

While ORR was comparable between treatment arms, more durable responses were observed with amivantamab-lazertinib versus osimertinib (26.1 vs 17.5 months). A favorable trend was also seen for OS and PFS2 in the amivantamab-lazertinib arm. The majority of participants in both arms who discontinued study treatment received a second-line therapy, with chemotherapy being the most common treatment type. TTD and TTST also showed favorable trends for amivantamab-lazertinib versus osimertinib.

The safety profile for amivantamab-lazertinib among Asian participants was consistent with that of the overall MARIPOSA population [33]. Participants in the amivantamab-lazertinib arm experienced higher rates of dose interruptions and reductions compared with the osimertinib arm, but this did not impact overall treatment efficacy [37]. Although amivantamab-lazertinib had higher rates of EGFR- and MET-related AEs and VTE compared with osimertinib, most were of grade 1 or 2 and occurred during the first 4 months of treatment. VTE is a known AE associated with lung cancer, with higher rates observed in patients with molecular driver alterations [38,39]. Furthermore, the vast majority of participants in MARIPOSA did not receive prophylactic anticoagulation [33]. In the PALOMA-3 and PALOMA-2 studies, the risk of VTE was effectively mitigated with prophylactic anticoagulation [40,41]. In addition, the use of a subcutaneous formulation of amivantamab may further reduce the risk of VTE and infusion-related reactions seen with amivantamab-lazertinib, with noninferior pharmacokinetics and efficacy to intravenous amivantamab [40].

5. Conclusions

In conclusion, this analysis of Asian participants enrolled in the MARIPOSA study showed that amivantamab-lazertinib offers a clinically meaningful PFS benefit compared with one of the commonly used treatment options, osimertinib. This result was consistent in predefined subgroups and with the overall population in MARIPOSA. OS and PFS2 data were not mature as of the data cutoff but showed a favorable trend for amivantamab-lazertinib. Safety was consistent with that of the overall population in MARIPOSA. Overall, amivantamab-lazertinib represents a new first-line standard of care in Asian patients with advanced NSCLC with common *EGFR* mutations.

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Clinical Trial Information

NCT04487080 (MARIPOSA).

Data 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 Open Data Access (YODA) Project site at https://yoda.yale.edu.

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Declaration of competing interest

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Appendix A. Supplementary data

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