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Research Paper

Overall survival for amivantamab plus lazertinib versus osimertinib as first-line treatment in Asian participants with *EGFR*-mutant advanced NSCLC: A MARIPOSA subset analysis

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ABSTRACT

Background: Approximately 60 % of lung cancer cases occur in Asia, indicating an epidemiological disparity and need for effective therapies. Amivantamab-lazertinib is approved for first-line *EGFR*-mutated advanced non-small cell lung cancer (NSCLC) in many countries. In the protocol-specified final overall survival (OS) analysis of MARIPOSA (NCT04487080), amivantamab-lazertinib showed a statistically significant and clinically meaningful improvement in OS versus osimertinib (HR, 0.75; $P = 0.005$) among all participants. We evaluated OS for amivantamab-lazertinib versus osimertinib in Asian participants.

Abbreviations: AE, adverse event; CI, confidence interval; CNS, central nervous system; DoR, duration of response; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; IRR, infusion-related reaction; MRI, magnetic resonance imaging; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, PFS after first subsequent therapy; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation; TTSP, time to symptomatic progression; TTST, time to subsequent therapy; VTE, venous thromboembolism.

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Patients and methods: Participants with previously untreated *EGFR*-mutated, locally advanced/metastatic NSCLC were randomized 2:2:1 to receive amivantamab-lazertinib, osimertinib, or lazertinib (for evaluating contribution of components). Self-identified Asian race was a stratification factor. OS was a key secondary endpoint.
Results: Of 1074 randomized participants, 629 self-identified as Asian (amivantamab-lazertinib:250; osimertinib:251; lazertinib:128). At a median follow-up of 38.7 months, amivantamab-lazertinib significantly prolonged OS versus osimertinib among Asian participants. Median OS was not reached (NR; 95 % CI, NR–NR) for amivantamab-lazertinib versus 38.4 months (95 % CI, 35.1–NR) for osimertinib (HR, 0.74; 95 % CI, 0.56–0.97; nominal $P = 0.026$). Assuming exponential distribution of OS in both arms, amivantamab-lazertinib is projected to prolong median OS among Asian participants by > 12 months versus osimertinib. At 36 months, 61 % and 53 % were alive in the amivantamab-lazertinib and osimertinib arms. Safety profile was consistent with the overall population.
Conclusions: Consistent with the overall population, amivantamab-lazertinib significantly improved OS versus osimertinib among Asian participants with previously untreated *EGFR*-mutated advanced NSCLC, making it the first regimen to improve survival among Asian patients.

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with a particularly high burden in Asia [1,2]. Globally, about 60 % of new lung cancer cases and 62 % of related deaths are observed in Asia [3]. Non-small cell lung cancer (NSCLC), the predominant type of lung cancer, often presents with activating mutations in the epidermal growth factor receptor (*EGFR*) gene [4,5], which occur more frequently in Asian (40 %–55 %) than in Western (15 %–25 %) populations [3]. Up to 90 % of *EGFR* mutations are either exon 19 deletions (Ex19del) or exon 21 L858R substitutions (L858R), collectively known as common *EGFR* mutations [6].

Currently, several targeted treatment options, including EGFR-tyrosine kinase inhibitors (TKIs), are available for the treatment of patients with advanced NSCLC harboring common *EGFR* mutations [7–9]. The third-generation EGFR-TKI, osimertinib, has demonstrated improved progression-free survival (PFS) over first- and second-generation EGFR-TKIs [10], and participants enrolled in the FLAURA trial demonstrated a median overall survival (OS) of approximately 3 years with osimertinib [11,12]. However, in the Asian subpopulation, no OS benefit (hazard ratio [HR], 1.00; 95 % confidence interval [CI], 0.75–1.32) was observed despite a significant benefit in the non-Asian subpopulation (HR, 0.54; 95 % CI, 0.38–0.77), underscoring the need for new treatment options for Asian patients [11]. Similarly, in Asian patients with common *EGFR*-mutated NSCLC, third-generation TKIs and EGFR-TKI–based combination therapies showed an OS benefit comparable to conventional chemotherapy, demonstrating a need for improved first-line targeted treatments for Asian patients [13,14]. Additionally, in the real-world setting, median OS among Asian patients receiving third-generation EGFR-TKIs ranged between 25.1–40.5 months across countries [15–17]. Moreover, treatment resistance is inevitable with third-generation EGFR-TKIs, with *MET* pathway activations, secondary *EGFR* alterations, and histologic transformations being the most frequent globally and in the Asian population [16,18–21]. Development of treatment resistance limits the long-term efficacy of third-generation EGFR-TKIs, as demonstrated by the substantial proportion (25 %–40 %) of patients of any race who do not receive second-line therapy after treatment with EGFR-TKI monotherapy, and pose challenges to subsequent therapy [22–24].

Recently, the combination regimen of osimertinib with chemotherapy demonstrated an improvement in PFS and OS compared with osimertinib monotherapy in the FLAURA2 study [25,26]. However, at the clinical cutoff date of January 8, 2024, osimertinib-chemotherapy demonstrated an OS benefit of only 2.2 months over osimertinib monotherapy (median OS, 40.5 months vs 38.3 months) among self-identified Asian participants [25,27]. At the clinical cutoff date of June 12, 2025, no OS benefit was observed in the Asian non-Chinese subpopulation (HR, 1.00; 95 % CI, 0.71–1.40), and although a numerical OS benefit was observed among the Asian Chinese subpopulation, this difference did not reach statistical significance (HR, 0.76; 95 % CI, 0.48–1.20) [28].

Amivantamab is an EGFR-MET bispecific antibody which exerts a triple mechanism of action by targeting EGFR and MET receptors and engaging in immune cell-directed activity through its optimized Fc domain [29–31]. Lazertinib is a highly selective central nervous system (CNS)–penetrant third-generation EGFR-TKI, which has demonstrated efficacy in both activating *EGFR* and T790M mutations [32,33]. In the protocol-specified final OS analysis of the phase 3 MARIPOSA study (NCT04487080; median follow-up, 37.8 months), amivantamab-lazertinib showed a statistically significant and clinically meaningful improvement in OS versus osimertinib (HR, 0.75; 95 % CI, 0.61–0.92; $P = 0.005$) among all randomized participants, reinforcing the superior efficacy findings observed with amivantamab-lazertinib in the primary analysis [34,35]. The median OS was not estimable (NE; 95 % CI, 42.9–NE) for amivantamab-lazertinib versus 36.7 months (95 % CI, 33.4–41.0) osimertinib with the benefit for amivantamab-lazertinib projected to exceed 1 year compared with osimertinib. Furthermore, amivantamab-lazertinib significantly reduced the incidences of *MET* (3.4 % vs 13.1 %; $P = 0.002$) and *EGFR* (1.4 % vs 7.6 %; $P = 0.01$) resistance alterations versus osimertinib, with no significant upregulation in other resistance pathways and a reduction in mutational heterogeneity, thereby demonstrating its ability to proactively address treatment resistance mechanisms [36].

Amivantamab-lazertinib is currently approved in the United States, Europe, and many countries in the Asia-Pacific region, including Australia, China, Japan, Singapore, South Korea, and Taiwan, as first-line treatment for patients with advanced NSCLC harboring *EGFR* Ex19del and L858R substitutions [37–44]. The approval in Asian participants was supported by the significantly prolonged median PFS (median follow-up, 22.5 months) observed with amivantamab-lazertinib versus osimertinib (HR, 0.65; 95 % CI, 0.50–0.83; $P < 0.001$) in a subgroup of Asian participants from MARIPOSA [45]. In this subgroup analysis after longer follow-up, we evaluated OS for amivantamab-lazertinib versus osimertinib among Asian participants in the MARIPOSA trial.

2. Methods

2.1. Study design and participants

Details of the trial design and methodology for MARIPOSA have been previously published [34,35]. Briefly, MARIPOSA enrolled participants 18 years of age or older with treatment-naïve locally advanced or metastatic NSCLC harboring common *EGFR* mutations (Ex19del or L858R). Participants with asymptomatic or previously treated and stable brain metastases were eligible. As reported previously, this analysis included participants from MARIPOSA who self-identified as “Asian”, including those reporting “mixed” race with any Asian heritage [45]. This trial was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International

Council for Harmonisation), relevant regulatory requirements, and Janssen Research & Development's bioethics policy. Participants gave written informed consent before enrollment, and the participating institutions provided Institutional Review Board approval.

2.2. Interventions

Participants were randomized (2:2:1) to receive amivantamab-lazertinib, osimertinib monotherapy, or lazertinib monotherapy. The lazertinib monotherapy arm assessed contribution of components. Primary results for all participants in the lazertinib monotherapy arm have been previously reported [34]. This analysis focuses on the amivantamab-lazertinib and osimertinib arms. Asian race (yes/no) was a stratification factor in MARIPOSA.

Amivantamab was administered intravenously weekly at a dose of 1050 mg (1400 mg in participants with a body weight $\geq$ 80 kg) for the first 4 weeks (Cycle 1), with the initial infusion split over 2 days (350 mg on Cycle 1 Day 1, and remainder on Cycle 1 Day 2). From Cycle 2 onward, the same amivantamab dose was administered every 2 weeks. Osimertinib (80 mg) and lazertinib (240 mg) were administered orally daily. Treatment crossover was not included in the study design, as second-line amivantamab-chemotherapy was not approved when the MARIPOSA study was designed [34,35].

2.3. Endpoints and assessments

OS was a key secondary endpoint in MARIPOSA that was prespecified with data collected prospectively. Time to symptomatic progression (TTSP), time to treatment discontinuation (TTD), time to subsequent therapy (TTST), investigator-assessed PFS after first subsequent therapy (PFS2), intracranial PFS, intracranial objective response rate (ORR), intracranial duration of response (DoR), and safety were also assessed as part of this analysis. Intracranial DoR was assessed from the time of first documented intracranial response until the time of intracranial progression or death. All other endpoints described here were assessed from the time of randomization. As a significant benefit of amivantamab–lazertinib over osimertinib was observed in the primary analysis, subsequent blinded independent central review of PFS, ORR, and DoR was not performed [34].

OS was defined as the time from randomization until death due to any cause. After treatment discontinuation or disease progression, OS and disease status were evaluated every 12 weeks ($\pm$2 weeks) until end of trial, death, loss to follow-up, or consent withdrawal. Participants without a recorded death at the time of analysis were censored based on the last recorded date the participant was known to be alive.

Intracranial outcomes were assessed in participants with a history of and/or measurable brain metastases by blinded independent central neuroradiologist review based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. As described previously, all participants had scheduled baseline CNS assessments using magnetic resonance imaging (MRI) of the brain. Follow-up imaging was conducted every 8 weeks ($\pm$1 week) for the first 30 months and every 12 weeks ($\pm$1 week) thereafter for participants with a history of brain metastases, or every 24 weeks ($\pm$1 week) for participants without a history of brain metastases. Serial brain MRIs were continued and analyzed until disease progression [35]. Participants who died or had not experienced intracranial disease progression were censored at their last evaluable intracranial disease assessment date; those with extracranial progression were not censored if brain MRIs continued.

Adverse events (AEs), vital signs, and laboratory tests were monitored at each visit and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0.

2.4. Statistical analysis

Details of the statistical methods employed in the overall population have been published previously [34,35].

This exploratory subgroup analysis was not included in formal hypothesis testing, and therefore, the *P* values for all endpoints are nominal. HRs and their corresponding 95 % CIs were calculated from a stratified Cox regression model with treatment as the sole explanatory variable. Median OS and corresponding 95 % CIs were estimated by the Kaplan-Meier method. Results of additional endpoints are reported as point estimates and 95 % CIs without adjustment for multiplicity and were analyzed using methods similar to the OS analysis. Median OS in the amivantamab-lazertinib group was projected using statistical methods described previously [35], and were further analyzed using 5 widely utilized parametric models (exponential, Weibull, generalized gamma, log-normal, log-logistic).

All results reported are based on the protocol-specified final OS analysis for the total population, with a clinical cutoff date of December 4, 2024. Participants stratified as Asian in the amivantamab-lazertinib and osimertinib arms were the focus of this subgroup analysis.

3. Results

3.1. Participants and treatment

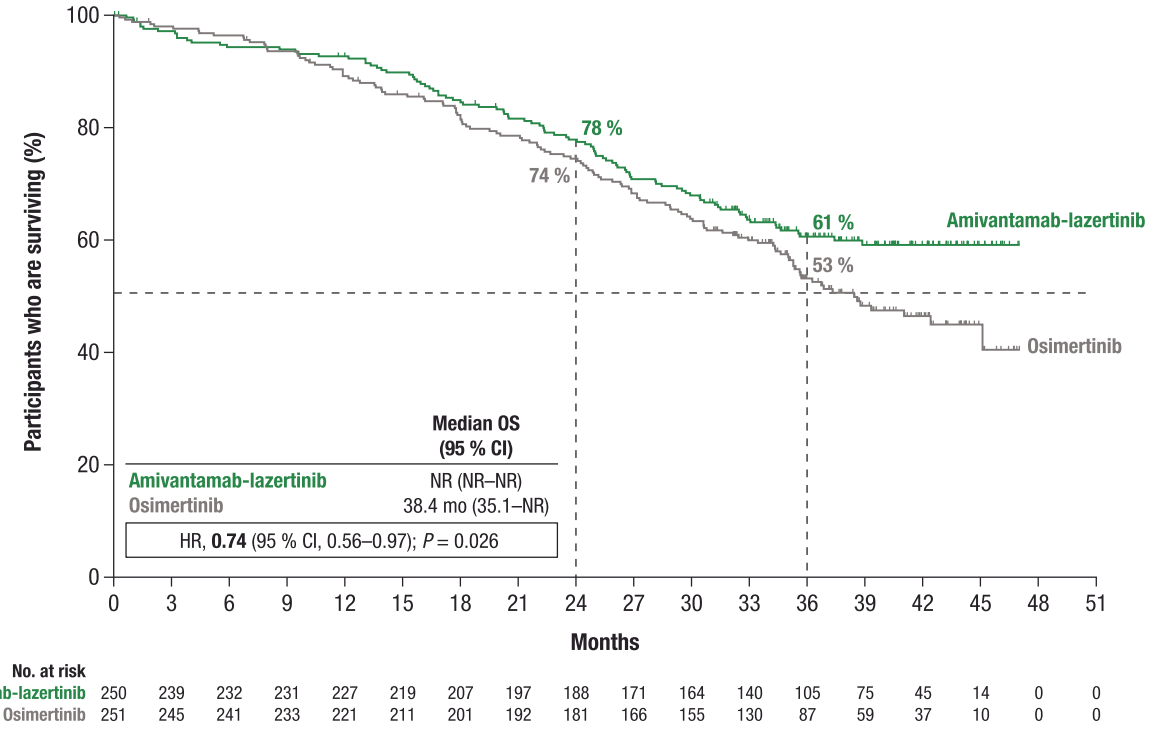
Between November 2020 through May 2022, 1074 participants were enrolled in MARIPOSA, of whom 629 self-identified as Asian (250 in amivantamab-lazertinib, 251 in osimertinib monotherapy, and 128 in lazertinib monotherapy; **Fig. S1**). A total of 625 (99 %) Asian participants received at least 1 dose of study treatment. Demographic and baseline disease characteristics among Asian participants were well-balanced between the amivantamab-lazertinib and osimertinib treatment arms, as described previously [45].

The median follow-up for this analysis was 38.7 months (range, 0.0–47.9). The median duration of treatment for Asian participants was 27.6 months (range, 0.2–47.2) in the amivantamab-lazertinib arm and 23.1 months (range, 0.2–47.2) in the osimertinib arm. At the clinical cutoff, 101 participants (41 %) in the amivantamab-lazertinib arm and 71 participants (28 %) in the osimertinib arm were still ongoing treatment.

3.2. Overall survival in Asian participants

At clinical cutoff, there were 96 deaths in amivantamab-lazertinib arm and 122 deaths in the osimertinib arm. Median OS was NR (95 % CI, NR–NR) in the amivantamab-lazertinib arm and 38.4 months (95 % CI, 35.1–NR) in the osimertinib arm (HR, 0.74; 95 % CI, 0.56–0.97; $P = 0.026$; Fig. 1A and Table 1). The OS rate at 36 months was 61 % (95 % CI, 54–67) for amivantamab-lazertinib and 53 % (95 % CI, 46–59) for osimertinib. In an exploratory analysis, based on the observed HR and median OS for osimertinib and with an exponential distribution assumption of OS in both arms, amivantamab-lazertinib is projected to provide a median OS benefit of > 12 months compared with osimertinib, which was further supported by 5 widely utilized parametric models, including baseline factors (**Supplementary Table S1**). OS favored amivantamab-lazertinib over osimertinib across the majority of predefined subgroups (Fig. 1B).

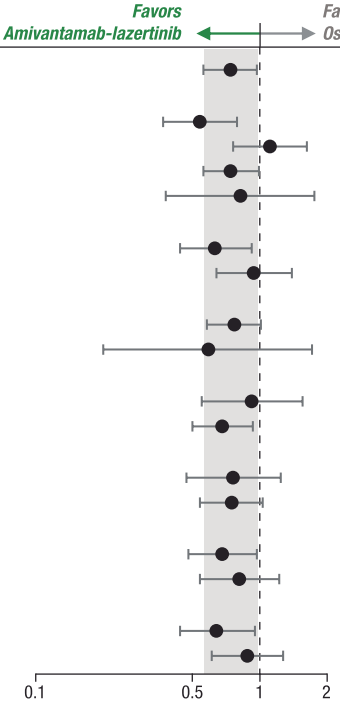
A.



No. at risk

Amivantamab-lazertinib	250	239	232	231	227	219	207	197	188	171	164	140	105	75	45	14	0	0
Osimertinib	251	245	241	233	221	211	201	192	181	166	155	130	87	59	37	10	0	0

B.



Subgroup	HR (95 % CI)[a]	N Amivantamab-lazertinib	N Osimertinib
All randomized Asian participants	0.74 (0.56–0.97)	250	251
Age category			
< 65 years	0.54 (0.37–0.79)	143	140
≥ 65 years	1.11 (0.76–1.62)	107	111
< 75 years	0.74 (0.56–0.99)	224	227
≥ 75 years	0.82 (0.38–1.75)	26	24
Sex			
Female	0.63 (0.44–0.92)	152	143
Male	0.94 (0.64–1.39)	98	108
Weight category			
< 80 kg	0.77 (0.58–1.01)	236	238
≥ 80 kg	0.59 (0.20–1.71)	14	13
ECOG PS score			
0	0.92 (0.55–1.55)	69	84
1	0.68 (0.50–0.93)	181	167
History of smoking			
Yes	0.76 (0.47–1.24)	70	70
No	0.75 (0.54–1.03)	180	181
History of brain metastases			
Yes	0.68 (0.48–0.97)	110	109
No	0.81 (0.54–1.22)	140	142
EGFR mutation			
Ex19del	0.64 (0.44–0.95)	137	139
L858R	0.88 (0.61–1.27)	112	112

Fig. 1. Overall survival in Asian participants (A) and subgroup analysis of overall survival among predefined subgroups of Asian participants (B) Note: Gray box indicates 95% CI of HR for all randomized participants. [a]Subgroup analyses were not part of the hypothesis testing of the trial and should not be used to infer definitive treatment effects. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; NR, not reached; OS, overall survival.

Table 1
Key efficacy endpoints in Asian participants.

Endpoint	Amivantamab-lazertinib (n = 250)	Osimertinib (n = 251)	Treatment effect (95 % CI)	*P* value
Overall survival				
Median (95 % CI) — mo	NR (NR–NR)	38.4 (35.1–NR)	0.74 (0.56–0.97)	0.026
Percentage of participants alive (95 % CI)				
At 12 mo	93 (89–95)	89 (85–92)	–	
At 24 mo	78 (72–83)	74 (69–79)	–	
At 36 mo	61 (54–67)	53 (46–59)	–	
Median time to symptomatic progression (95 % CI) — mo	NR (37.4–NR)	30.8 (26.7–35.6)	0.65 (0.51–0.84)	< 0.001
Median time to treatment discontinuation (95 % CI) — mo	27.9 (22.8–34.6)	23.2 (20.9–26.0)	0.74 (0.60–0.93)	0.008
Median time to subsequent therapy (95 % CI) — mo	33.6 (28.1–NR)	25.4 (22.6–28.9)	0.70 (0.56–0.88)	0.002
Median progression-free survival after first subsequent therapy (95 % CI) — mo	NR (38.9–NR)	34.2 (29.9–38.8)	0.70 (0.54–0.91)	0.007
Intracranial progression-free survival[a]				
Median (95 % CI) — mo	23.5 (18.4–32.8)	23.9 (18.4–28.9)	0.79 (0.57–1.09)	0.155
Percentage of participants alive and free from intracranial progression (95 % CI)				
At 12 mo	74 (64–81)	77 (68–84)	–	
At 24 mo	50 (40–59)	50 (40–59)	–	
At 36 mo	36 (27–46)	18 (10–27)	–	
Intracranial objective response (95 % CI) — %[b]	78 (69–85)	79 (70–86)	0.92 (0.48–1.76)[c]	0.801
Median duration of intracranial objective response (95 % CI) — %[d]	NR (25.8–NR)	27.4 (22.1–NR)	–	

BICR, blinded independent central review; CI, confidence interval; NR, not reached.
[a]Among participants with a history of brain metastasis. Included 110 participants in the amivantamab-lazertinib group and 109 participants in the osimertinib group. [b]Included 108 participants in the amivantamab-lazertinib group and 110 participants in the osimertinib group with intracranial disease at baseline. Participants who had a history of brain metastases and underwent surgery were not included. [c]Reported as an odds ratio. [d]Among confirmed responders (complete response + partial response) with intracranial disease at baseline as evaluated by BICR. Included 75 participants in the amivantamab-lazertinib group and 78 participants in the osimertinib group.

3.3. Additional outcomes in Asian participants

The median TTSP was prolonged with amivantamab-lazertinib (NR; 95 % CI, 37.4–NR) than with osimertinib (30.8 months; 95 % CI, 26.7–35.6) with a HR of 0.65 (95 % CI, 0.51–0.84; $P < 0.001$; **Supplementary Fig. S2**). Median TTD was 27.9 months (95 % CI, 22.8–34.6) for amivantamab-lazertinib and 23.2 months (95 % CI, 20.9–26.0) for osimertinib (HR, 0.74; 95 % CI, 0.60–0.93; $P = 0.008$; **Supplementary Fig. S3**). Median TTST was 33.6 months (95 % CI, 28.1–NR) and 25.4 months (95 % CI, 22.6–28.9) in the amivantamab-lazertinib and osimertinib arms, respectively (HR, 0.70; 95 % CI, 0.56–0.88; $P = 0.002$; **Supplementary Fig. S4**).

Overall, 97 participants (39 %) in the amivantamab-lazertinib arm and 154 (61 %) in the osimertinib group had disease progression and discontinued the assigned treatment. Of these participants, 71 % in the amivantamab-lazertinib arm and 75 % in the osimertinib arm received subsequent anticancer therapy. Chemotherapy- and TKI-based regimens were the most commonly received subsequent therapy class for amivantamab-lazertinib, while the majority of participants in the osimertinib arm received chemotherapy-based regimens as their next line of therapy (Fig. 2A). Median PFS2 was NR (95 % CI, 38.9–NR) in the amivantamab-lazertinib arm and 34.2 months (95 % CI, 29.9–38.8) in the osimertinib arm (HR, 0.70; 95 % CI, 0.54–0.91; $P = 0.007$; Fig. 2B and Table 1).

3.4. Intracranial outcomes in Asian participants

Among Asian participants who had a history of brain metastases, 36 % of participants in the amivantamab-lazertinib arm versus 18 % of those in the osimertinib arm were alive and free from intracranial disease progression at 36 months; the intracranial PFS curves continue to widen over time (Fig. 3A and Table 1). Among those with measurable baseline brain lesions (108 for amivantamab-lazertinib and 110 for osimertinib), intracranial ORR was 78 % (95 % CI, 69–85) in the amivantamab-lazertinib arm and 79 % (95 % CI, 70–86) in the osimertinib arm. Intracranial responses were confirmed in 69 % (75/108) and 71 % (78/110) of participants in the amivantamab-lazertinib and osimertinib arms, respectively. Among participants with confirmed responses, the median intracranial DoR was NR (95 % CI, 25.8–NR) in the amivantamab-lazertinib arm and 27.4 months (95 % CI, 22.1–NR) in the osimertinib arm (Fig. 3B and Table 1).

3.5. Safety in Asian participants

The safety profile of amivantamab-lazertinib was consistent with the prior report in Asian participants and the overall population [34,35,45]. The most commonly reported AEs were related to EGFR and MET inhibition (Table 2). Grade ≥ 3 AEs occurred in 78 % and 49 % of participants in the amivantamab-lazertinib and osimertinib arms, respectively. For the majority of key AEs, first onset occurred in the first 4 months (**Supplementary Fig. S5**). No new safety signals were identified with longer follow-up in the Asian population. Serious adverse events (SAEs) were reported in 56 % and 40 % of participants in the amivantamab-lazertinib and osimertinib arms, respectively (Table 2), with all SAEs occurring in at least 1 % of participants reported in **Supplementary Table S2**. Venous thromboembolism (VTE) was reported in 34 % of participants in the amivantamab-lazertinib arm and 7 % in the osimertinib arm. Of note, only 3 (1 %) participants and 9 (4 %) participants in the amivantamab-lazertinib and osimertinib arms, respectively, were receiving anticoagulation at baseline (as currently recommended per the amivantamab-lazertinib label). The incidence of pneumonitis was low in both arms (~2% each). Serious interstitial lung disease was reported in 5 (2 %) participants in the amivantamab-lazertinib arm and 3 (1 %) participants in the osimertinib arm.

4. Discussion

In this Asian subset analysis of MARIPOSA, amivantamab-lazertinib significantly reduced the risk of death compared with osimertinib (HR, 0.74; 95 % CI, 0.56–0.97; $P = 0.026$). Median OS was NR (95 % CI, NR–NR) versus 38.4 months (95 % CI, 35.1–NR) with amivantamab-lazertinib versus osimertinib, with a projected OS benefit of > 1 year. The curves separate at approximately 12 months and widen over time as evidenced by a 4 % difference in the 2-year OS rates for amivantamab-lazertinib versus osimertinib (78 % vs 74 %), which doubled to 8 % at 3 years (61 % vs 53 %). OS favored amivantamab-lazertinib in nearly all key prespecified subgroups of the Asian subpopulation. Based on these results, amivantamab-lazertinib is the only regimen to improve survival

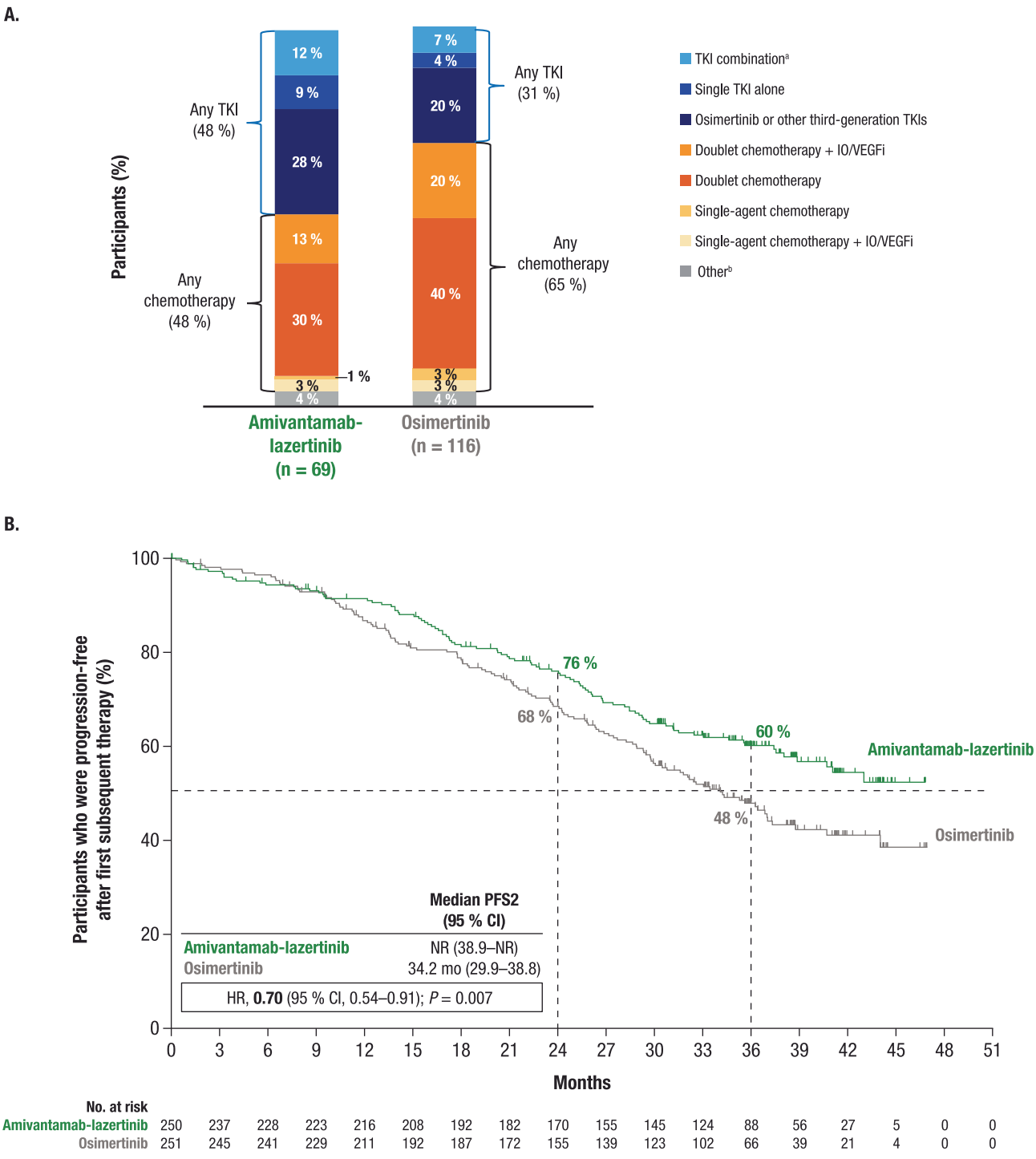


Fig. 2. First subsequent therapies (A) and progression-free survival after first subsequent therapy (B) in Asian participants Note: In the osimertinib group: 1 participant received subsequent treatment with quadruplet chemotherapy and is included in the doublet chemotherapy category; 1 participant received triplet chemotherapy + IO/VEGFi and is included in the doublet chemotherapy + IO/VEGFi category. Percentages may not sum because of rounding. [a]TKI combination includes TKI + chemotherapy (8 % for amivantamab-lazertinib and 5 % for osimertinib). [b]Other therapies included IO alone, herbal supplements, amivantamab (1 participant who received osimertinib during the trial received amivantamab monotherapy as a first subsequent therapy), and investigational agents. CI, confidence interval; HR, hazard ratio; IO, immuno-oncology; NR, not reached; PFS2, progression-free survival after first subsequent therapy; TKI, tyrosine kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

outcomes among Asian participants.

The significantly improved survival outcomes observed among Asian participants may be associated with amivantamab's demonstrated ability to significantly reduce and proactively address both *EGFR*- and *MET*-based acquired resistance to treatment with third-generation TKIs and its potential immune cell–directing activity [18–20,36]. As a substantial proportion of patients do not receive any second-line treatments [22–24], it is critical to select the best first-line regimen that mitigates development of prevalent acquired resistance mechanisms, thereby sustaining disease control and reserving chemotherapy for subsequent lines, when resistance profiles are generally more heterogeneous and complex.

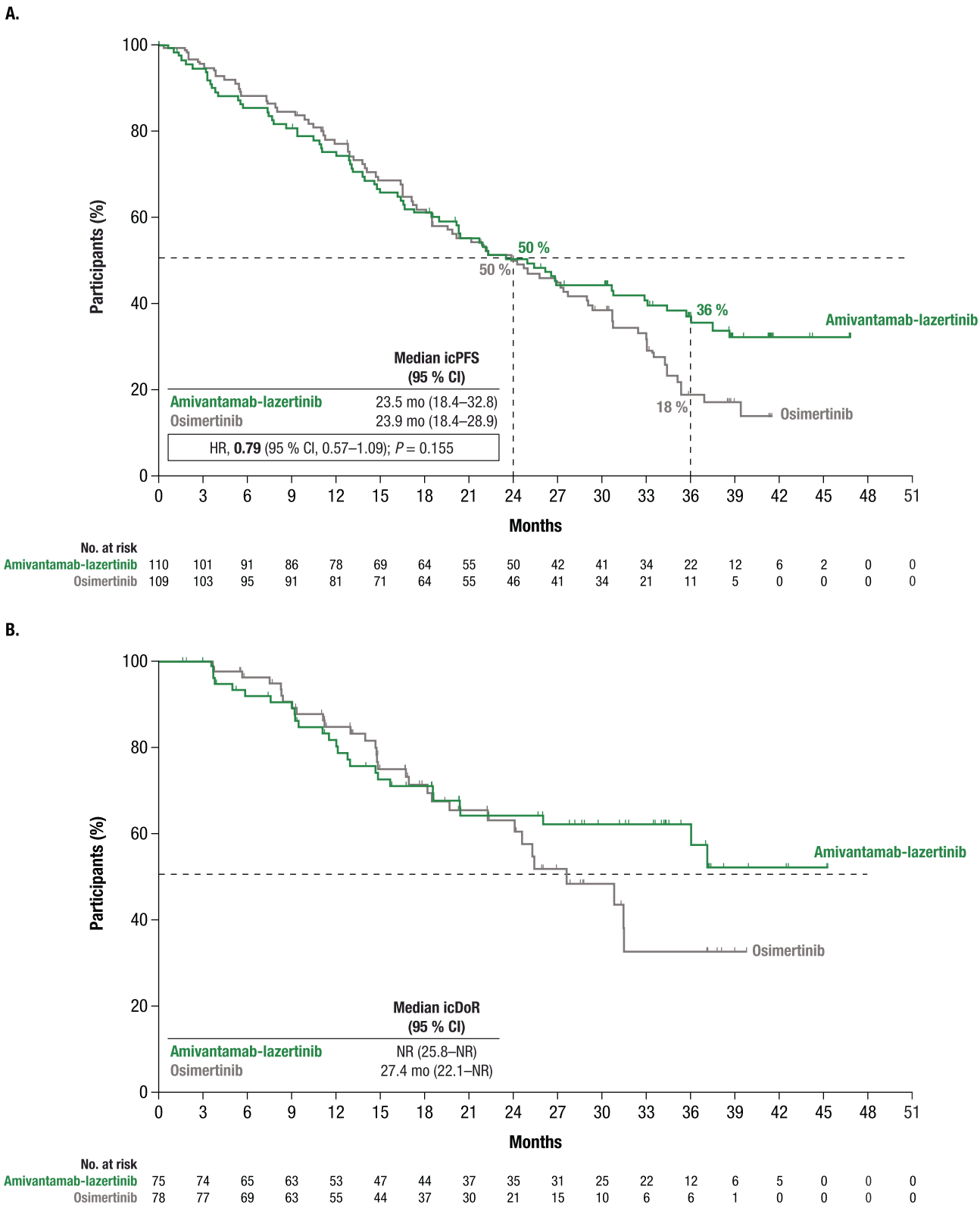


Fig. 3. Intracranial progression-free survival[a] (A) and duration of intracranial response[b] (B) in Asian participants [a]Among participants with a history of brain metastasis measured by BICR. [b]Among confirmed responders (confirmed PR + confirmed CR) with intracranial disease at baseline as measured by BICR. BICR, blinded independent central review; CI, confidence interval; CR, complete response; HR, hazard ratio; icDoR, intracranial duration of response; icPFS, intracranial progression-free survival; NR, not reached; PR, partial response.

Table 2
Adverse events in the safety population of Asian participants.

Adverse event, n (%)	Amivantamab-lazertinib (n = 248)		Osimertinib (n = 250)	
	All	Grade ≥ 3	All	Grade ≥ 3
Any adverse event	248 (100)	193 (78)	248 (99)	122 (49)
Any serious adverse event	139 (56)	–	99 (40)	–
Any adverse event resulting in death	–	19 (8)	–	14 (6)
Adverse events reported in ≥ 15 % of the participants in either group[a]				
Paronychia	185 (75)	22 (9)	83 (33)	2 (1)
Rash	162 (65)	44 (18)	86 (34)	2 (1)
Infusion-related reaction	158 (64)	7 (3)	0	0
Hypoalbuminemia	150 (60)	20 (8)	21 (8)	0
Increased alanine aminotransferase	102 (41)	13 (5)	46 (18)	4 (2)
Increased aspartate aminotransferase	92 (37)	9 (4)	51 (20)	4 (2)
Peripheral edema	89 (36)	3 (1)	14 (6)	0
Constipation	87 (35)	0	46 (18)	0
Stomatitis	85 (34)	3 (1)	79 (32)	1 (< 1)
COVID-19	77 (31)	4 (2)	69 (28)	5 (2)
Decreased appetite	76 (31)	4 (2)	48 (19)	3 (1)
Dermatitis acneiform	74 (30)	22 (9)	36 (14)	0
Diarrhea	71 (29)	4 (2)	109 (44)	1 (< 1)
Anemia	70 (28)	12 (5)	60 (24)	7 (3)
Pruritus	59 (24)	1 (< 1)	56 (22)	0
Nausea	55 (22)	3 (1)	28 (11)	0
Hypocalcemia	55 (22)	8 (3)	26 (10)	0
Hypokalemia	52 (21)	14 (6)	29 (12)	2 (1)
Cough	50 (20)	0	57 (23)	0
Dry skin	49 (20)	1 (< 1)	40 (16)	1 (< 1)
Thrombocytopenia	48 (19)	4 (2)	53 (21)	6 (2)
Dizziness	43 (17)	0	24 (10)	0
Fatigue	42 (17)	3 (1)	20 (8)	2 (1)
Pulmonary embolism[b]	42 (17)	16 (6)	11 (4)	4 (2)
Pyrexia	38 (15)	0	39 (16)	0
Increased gamma-glutamyltransferase	37 (15)	5 (2)	14 (6)	2 (1)
Myalgia	37 (15)	2 (1)	14 (6)	0
Paresthesia	37 (15)	2 (1)	13 (5)	0
Muscle spasms	36 (15)	1 (< 1)	18 (7)	0
Decreased weight	32 (13)	2 (1)	39 (16)	4 (2)
Leukopenia	24 (10)	1 (< 1)	54 (22)	2 (1)
Increased blood creatinine	22 (9)	1 (< 1)	40 (16)	0
Neutropenia	19 (8)	4 (2)	45 (18)	6 (2)

[a]Listed in descending order based on the amivantamab-lazertinib group. [b]Venous thromboembolism (a grouped term that included pulmonary embolism, deep-vein thrombosis, limb venous thrombosis, venous thrombosis, thrombosis, superficial-vein thrombosis, thrombophlebitis, embolism, venous embolism, jugular-vein thrombosis, sigmoid-sinus thrombosis, axillary-vein thrombosis, pulmonary infarction, vena cava thrombosis, central venous catheterization, portal-vein thrombosis, the post-thrombotic syndrome, pulmonary thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, pelvic venous thrombosis, and the superior vena cava syndrome) occurred in 34 % of participants in the amivantamab–lazertinib group and in 7 % of participants in the osimertinib group. Venous thromboembolism can be managed with prophylactic anticoagulation for the first 4 months of treatment and in accordance with local guidelines.

In this analysis, 41 % of Asian participants in the amivantamab-lazertinib arm and 28 % in the osimertinib arm were still ongoing treatment at 3 years, demonstrating that long-term treatment with amivantamab-lazertinib is feasible. The majority of participants in both arms who had disease progression and discontinued treatment went on to receive a subsequent therapy (71 % for amivantamab-lazertinib and 75 % for osimertinib). Asian participants in both arms received chemotherapy-based or TKI-based regimens as their first subsequent therapy. Furthermore, consistent with the overall population, amivantamab-lazertinib also prolonged median TTD, TTST, and PFS2. In addition to longer survival, symptomatic progression was delayed in participants who received amivantamab-lazertinib versus osimertinib as demonstrated by prolonged TTSP, a patient-relevant endpoint measuring time from randomization to the onset of new/worsening lung cancer symptoms necessitating a change in therapy, clinical intervention, or death, whichever comes first [35].

Patients with NSCLC harboring *EGFR* mutations are more susceptible to brain metastases compared to those without [46–49]. Furthermore, patients may develop brain metastases as the disease progresses. Among Asian patients with *EGFR*-mutated NSCLC, the rate of brain metastases is between 31 %-42 % [47,50], consistent with the rate observed in Asian participants enrolled in MARIPOSA (~44 %) [45]. Consequently, MARIPOSA conducted serial brain MRIs for all participants, which demonstrated numerically improved CNS disease control among Asian participants who received amivantamab-lazertinib. At 36 months, twice as many Asian participants with a history of brain metastases in the amivantamab-lazertinib group versus osimertinib group were alive and free from intracranial disease progression (36 % versus 18 %), consistent with the intracranial outcomes seen in the overall population. Furthermore, the intracranial PFS curves for amivantamab-lazertinib and osimertinib diverge after approximately 1 year of treatment, indicating sustained efficacy of first-line amivantamab-lazertinib and its impact on the underlying disease biology and long-term treatment outcomes.

The safety profile of amivantamab-lazertinib in Asian participants remained consistent with the primary analysis in the Asian population [45], as well as the overall population [34], with no new safety signals observed. Since the primary analysis there was no meaningful increase in VTE rates, which supports the concept that VTE is predominantly an early event with amivantamab-lazertinib treatment. Notably, MARIPOSA did not incorporate enhanced prophylactic strategies for managing common AEs, which were later developed based on observations from MARIPOSA. Prophylactic regimens to mitigate dermatologic AEs and VTEs were evaluated in the COCOON (NCT06120140) study. The COCOON dermatologic regimen, consisting of prophylactic oral doxycycline or minocycline (100 mg), clindamycin 1 % on the scalp, chlorhexidine 4 % for paronychia prophylaxis, and skin moisturization,

significantly reduced grade ≥ 2 dermatologic AEs associated with intravenous amivantamab compared with standard dermatologic management (42 % vs 75 %; $P < 0.001$) [51]. Among Asian participants, subgroup analysis demonstrated an odds ratio of 0.22 (95 % CI, 0.10–0.47) favoring the COCOON dermatologic regimen versus standard dermatologic management for reducing the incidence of grade ≥ 2 dermatologic AEs of interest [51]. In addition, preliminary findings from the COCOON treatment substudy, evaluating the reactive management of dermatologic AEs in patients undergoing amivantamab-lazertinib therapy, demonstrated that 63 % of participants responded to tacrolimus treatment with substantial improvement in dermatologic AEs of interest, suggesting that the use of 0.1 % tacrolimus ointment may represent an effective intervention for reactive management of dermatologic AEs that occur despite the COCOON regimen [52]. Furthermore, all participants in the COCOON study received prophylactic anticoagulation for the first 4 months of treatment resulting in a VTE incidence of 13 % in both arms of the study [51], which is comparable with the rate of VTE in patients with stage IV NSCLC [53].

Regimens to address infusion-related reactions (IRRs) were evaluated in the SKIPPirr (NCT05663866) study and demonstrated an approximately 3-fold reduction in IRRs in participants receiving intravenous amivantamab, when oral dexamethasone 8 mg twice daily prophylaxis was added to standard prophylaxis [54]. The subcutaneous formulation of amivantamab, which is currently approved in the United States, Europe, China, and Japan, also substantially reduced IRRs (13 % vs 66 %) and treatment administration time (<5 min vs up to 5 h) compared with the intravenous formulation [55–59]. Combining subcutaneous amivantamab with VTE and dermatologic prophylactic regimens may enhance the overall treatment experience with amivantamab-lazertinib and potentially further improve outcomes.

In conclusion, amivantamab-lazertinib is the first treatment regimen to demonstrate a significant OS advantage in the Asian population since the introduction of first- and second-generation EGFR-TKIs. Consistent with the overall population in MARIPOSA, amivantamab-lazertinib significantly reduced the risk of death compared with osimertinib among Asian participants with previously untreated *EGFR*-mutated advanced NSCLC and is projected to provide an OS benefit of > 1 year. These results further establish amivantamab-lazertinib as the new first-line standard of care among all patients, including those of Asian race.

Conflicts of Interest

Hidetoshi Hayashi: **consulting or advisory role** for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo/UCB Japan, and Janssen; **patents, royalties, or other intellectual property** for Sysmex; **honoraria** from AbbVie, Amgen, AstraZeneca Japan, BioPharma, Boehringer Ingelheim, Bristol Myers Squibb Japan, Chugai Pharma, Daiichi Sankyo/UCB Japan, Eli Lilly, Guardant Health, Hisamitsu, Janssen, Kyowa Kirin, Merck, Merck Sharp & Dohme, Nihon, Nippon Kayaku, Novartis, Novocure, Ono Pharmaceutical, Pfizer, and Takeda; **research funding** from A2 Healthcare Corp., AbbVie Inc., Amgen Inc., Ascent Development Services, Astellas Pharma Inc., AstraZeneca K.K., Bayer Yakuhin Ltd., Bristol-Myers Squibb Company, Chugai Pharmaceutical Co. Ltd., CMIC Co. Ltd., Clinical Research Support Center Kyushu, Comprehensive Support Project for Oncological Research of Breast Cancer, Covance Japan Inc., Daiichi Sankyo Co. Ltd., Eisai Co. Ltd., Eisai Inc., Eli Lilly Japan K.K., EP-CRSU Co. Ltd., EPS Corporation, GlaxoSmithKline K.K., IQVIA Services Japan K.K., Janssen Pharmaceutical K.K., Japan Clinical Cancer Research Organization, Japan Clinical Research Operations Medical Research Support, Japanese Gastric Cancer Association, Thoracic Oncology Research Group, Kobayashi Pharmaceutical Co. Ltd., Kyowa Kirin Co. Ltd., Labcorp Development Japan K.K., Mebix Inc., Medpace Japan K.K., Merck Biopharma Co. Ltd., Mochida Pharmaceutical Co., Ltd., MSD K.K., Nippon Boehringer Ingelheim Co. Ltd., Nippon Kayaku Co. Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Pfizer Japan Inc., Pfizer R&D Japan G.K., ICON (formerly PRA Health Sciences Inc.), Sanofi K.K., Shionogi & Co. Ltd., SRL Medisearch Inc., Syneos Health Clinical K.K., Taiho Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., and West Japan Oncology Group Byoung Chul Cho: **consulting role** for Amgen, ArriVent, AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, CJ Bioscience, Cyrus Therapeutics, Gilead, GSK, Regeneron, Johnson & Johnson, MSD, and Yuhan; served on an **advisory board** for KANAPH Therapeutic Inc, Cyrus therapeutics, and J INTS BIO; **leadership roles** for DAAN Biotherapeutics (Founder) and J INTS BIO; **patents, royalties, or other intellectual property** for Champions Oncology, Crown Bioscience, Imagen, and PearlRiver Bio GmbH; **stock or other ownership interests** with J INTS BIO and KANAPH Therapeutics Inc.; **research funding** from CJ Bioscience, Cyrus, Dong-A ST, ImmuneOncia, J INTS BIO, Johnson & Johnson, Ligachem bioscience, MSD, and Yuhan; **invited speaker** for ASCO, AstraZeneca, ESMO, Guardant, IASLC, Korean Cancer Association, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, MSD, Pfizer, Roche, The Chinese Thoracic Oncology Society, and Zailab. 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6. Data sharing statement

The data sharing policy of Johnson & Johnson is available at https://innovativemedicine.jnj.com/our-innovation/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 http://yoda.yale.edu.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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