ORIGINAL ARTICLE

Amivantamab plus Lazertinib in Previously Untreated *EGFR*-Mutated Advanced NSCLC

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ABSTRACT

BACKGROUND

Amivantamab plus lazertinib (amivantamab–lazertinib) has shown clinically meaningful and durable antitumor activity in patients with previously untreated or osimertinib-pretreated *EGFR* (epidermal growth factor receptor)–mutated advanced non–small-cell lung cancer (NSCLC).

METHODS

In a phase 3, international, randomized trial, we assigned, in a 2:2:1 ratio, patients with previously untreated *EGFR*-mutated (exon 19 deletion or L858R), locally advanced or metastatic NSCLC to receive amivantamab–lazertinib (in an open-label fashion), osimertinib (in a blinded fashion), or lazertinib (in a blinded fashion, to assess the contribution of treatment components). The primary end point was progression-free survival in the amivantamab–lazertinib group as compared with the osimertinib group, as assessed by blinded independent central review.

RESULTS

Overall, 1074 patients underwent randomization (429 to amivantamab–lazertinib, 429 to osimertinib, and 216 to lazertinib). The median progression-free survival was significantly longer in the amivantamab–lazertinib group than in the osimertinib group (23.7 vs. 16.6 months; hazard ratio for disease progression or death, 0.70; 95% confidence interval [CI], 0.58 to 0.85; P<0.001). An objective response was observed in 86% of the patients (95% CI, 83 to 89) in the amivantamab–lazertinib group and in 85% of those (95% CI, 81 to 88) in the osimertinib group; among patients with a confirmed response (336 in the amivantamab–lazertinib group and 314 in the osimertinib group), the median response duration was 25.8 months (95% CI, 20.1 to could not be estimated) and 16.8 months (95% CI, 14.8 to 18.5), respectively. In a planned interim overall survival analysis of amivantamab–lazertinib as compared with osimertinib, the hazard ratio for death was 0.80 (95% CI, 0.61 to 1.05). Predominant adverse events were *EGFR*-related toxic effects. The incidence of discontinuation of all agents due to treatment-related adverse events was 10% with amivantamab–lazertinib and 3% with osimertinib.

CONCLUSIONS

Amivantamab–lazertinib showed superior efficacy to osimertinib as first-line treatment in *EGFR*-mutated advanced NSCLC. (Funded by Janssen Research and Development; MARIPOSA ClinicalTrials.gov number, NCT04487080.)

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*A complete list of the investigators in the MARIPOSA trial is provided in the Supplementary Appendix, available at NEJM.org.

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Activating mutations in the epidermal growth factor receptor gene (*EGFR*) are estimated to be present in 15 to 50% of nonsquamous advanced non–small-cell lung cancers (NSCLCs).[1,2] Among *EGFR* mutations, 85 to 90% are exon 19 deletions (Ex19del) or exon 21 codon p.Leu858Arg (L858R) substitutions.[3,4] The current first-line therapy for Ex19del and L858R advanced NSCLC is osimertinib, which is a third-generation EGFR–tyrosine kinase inhibitor (EGFR-TKI).[5,6] In the phase 3 FLAURA trial, osimertinib therapy improved progression-free survival as compared with first-generation EGFR-TKIs.[7] Other third-generation EGFR-TKIs have since been approved.[8,9] Resistance to third-generation EGFR-TKIs eventually develops in nearly all patients; the mechanisms of resistance are diverse and polyclonal.[10-12] The most common measurable resistance mechanisms are secondary *EGFR* pathway alterations and *MET* pathway activation; however, up to 50% of patients do not have an identified resistance mechanism to osimertinib,[13] which makes the selection of subsequent treatment challenging.

Amivantamab, an EGFR-MET bispecific antibody with immune cell–directing activity, has unique mechanisms of action, including ligand blocking, receptor degradation, and engagement of immune effector cells (monocytes, macrophages, and natural killer cells) by means of its optimized Fc domain.[14-17] First-line amivantamab plus chemotherapy (amivantamab–chemotherapy) and second-line amivantamab monotherapy are approved for patients with *EGFR* exon 20 insertion–mutated advanced NSCLC.[18,19] Amivantamab–chemotherapy has also significantly improved progression-free survival as compared with chemotherapy in patients who had received osimertinib for NSCLC.[20] In addition, activity of amivantamab monotherapy was seen in patients with *MET* exon 14 skipping mutations and *MET* amplification.[21,22]

Lazertinib is a highly selective, central nervous system (CNS)–penetrant, third-generation EGFR-TKI that has shown efficacy in both activating *EGFR* and p.Thr790Met (T790M) mutations.[23,24] Lazertinib is selective for mutated *EGFR*, which means that the safety profile indicates that this drug is suitable for use in combination therapy.[25-27] In the phase 3 LASER301 trial, first-line treatment with lazertinib improved progression-free survival as compared with gefitinib among patients with *EGFR*-mutated advanced NSCLC.[28]

Amivantamab was combined with lazertinib initially in patients whose disease had progressed during or after osimertinib therapy.[29,30] Amivantamab–lazertinib had clinical activity across a wide range of secondary *EGFR* and *MET* alterations, including in patients without an identified mechanism of resistance. It was hypothesized that first-line treatment with amivantamab–lazertinib could proactively address downstream resistance mechanisms and improve clinical outcomes. Amivantamab–lazertinib therapy was evaluated in patients with previously untreated *EGFR*-mutated advanced NSCLC in the phase 1 CHRYSALIS trial.[31] All 20 enrolled patients had a response, and at a median follow-up of 33.6 months, 50% of the patients had an ongoing response and were continuing to receive treatment. At 36 months, 51% of the patients were free from disease progression, and 85% were alive.

We conducted the phase 3, international, randomized MARIPOSA trial to assess the efficacy and safety of amivantamab–lazertinib as compared with osimertinib alone as first-line treatment in patients with *EGFR*-mutated advanced NSCLC. In a third group in this trial, lazertinib monotherapy was administered to patients in order to evaluate the contribution of the components in the combination treatment.

Methods

Patients

In this trial, we enrolled patients 18 years of age or older with previously untreated locally advanced or metastatic NSCLC with a common *EGFR* mutation (Ex19del or L858R). Asymptomatic or stable brain metastases were allowed. Additional inclusion and exclusion criteria are discussed in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Oversight

The 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), applicable regulatory requirements, and the policy on bioethics and human biologic samples of the trial sponsor, Janssen Research and Development. The trial was designed by representatives of the sponsor, which was responsible for the collection and

analysis of the data and the interpretation of the data 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 trial to the protocol, available at NEJM.org.

TRIAL DESIGN AND TREATMENT

Patients were randomly assigned in a 2:2:1 ratio to receive amivantamab–lazertinib, osimertinib monotherapy, or lazertinib monotherapy (Fig. S1 in the Supplementary Appendix). Intravenous amivantamab was administered weekly at a dose of 1050 mg (or 1400 mg in patients with a body weight of ≥80 kg) for the first 4 weeks (cycle 1), with the first infusion split over a period of 2 days (with 350 mg given on cycle 1 day 1, and the remainder given 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 taken orally daily.

Treatment blinding for the amivantamab–lazertinib group was not feasible owing to differences in routes of administration. The osimertinib and lazertinib monotherapies were administered in a double-blind manner. Randomization was stratified according to *EGFR* mutation type (Ex19del or L858R), Asian race (yes or no), and history of brain metastases (yes or no).

END POINTS

The primary end point was progression-free survival in the amivantamab–lazertinib group as compared with the osimertinib group, as determined on the basis of blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[32] The key secondary end point was overall survival. Other secondary end points included objective response (defined as a complete or partial response), duration of response, and safety. A complete list of the end points and their definitions are provided in the protocol.

ASSESSMENTS

Disease assessments (by means of computed tomography and magnetic resonance imaging [MRI]) were performed within 28 days before randomization (baseline), then every 8 weeks (within a window of ±1 week) for the first 30 months, and every 12 weeks (window, ±1 week) thereafter until disease progression. All the assessments were performed by means of blinded independent central review according to the RECIST, version 1.1, definitions.

According to the protocol, all the patients underwent scheduled CNS assessments by means of MRI of the head. Imaging of the head was done at baseline, with subsequent imaging (until disease progression) occurring every 8 weeks (window, ±1 week) for the first 30 months and then every 12 weeks (window, ±1 week) in patients with a history of brain metastases or every 24 weeks (window, ±1 week) in patients without a history of brain metastases.

Survival, subsequent treatment, and disease status were assessed every 12 weeks (window, ±2 weeks) after the discontinuation of treatment or disease progression (whichever occurred first) until the end of the trial, death, loss to follow-up, or withdrawal of consent. Adverse events, vital signs, and laboratory tests were assessed at each visit and graded with the use of the Common Terminology Criteria for Adverse Events, version 5.0, of the National Cancer Institute.

STATISTICAL ANALYSIS

Efficacy analyses included all the patients who had undergone randomization. Safety analyses included all the patients in the efficacy-analysis population who had received at least one dose of any trial treatment. For the calculation of progression-free survival, we estimated that a sample of at least 800 patients with 450 events across the amivantamab–lazertinib and osimertinib groups would provide the trial with 90% power to detect a hazard ratio for progression or death of 0.73 with a two-sided alpha of 0.05. The estimation corresponded to an extension of at least 7 months in median progression-free survival (estimated at 26 months in the amivantamab–lazertinib group and 19 months in the osimertinib group).

Primary hypothesis testing of amivantamab–lazertinib as compared with osimertinib in the progression-free survival analysis was evaluated by means of the P value generated from the stratified log-rank test, with *EGFR* mutation type, Asian race, and history of brain metastases as stratification factors. The hazard ratio and 95% confidence intervals were estimated with the use of a

stratified Cox regression model, with treatment as the sole explanatory variable. Medians and corresponding 95% confidence intervals were estimated with the use of the Kaplan–Meier method. A hierarchical hypothesis-testing approach was used: progression-free survival, and then overall survival. An interim analysis of overall survival was planned to be conducted at the time of the primary analysis of progression-free survival. Full statistical details are provided in the statistical analysis plan (see the protocol).

Analyses of additional secondary or other end points, including subgroup analyses, were not part of the hypothesis testing of the trial. Results of these analyses are reported as point estimates and 95% confidence intervals without adjustment for multiplicity and should not be used to infer definitive treatment effects. All the data reported here are based on the primary analysis, which focused on the comparison of amivantamab–lazertinib with osimertinib, at a data-cutoff date of August 11, 2023.

RESULTS

PATIENTS AND TREATMENT

From November 2020 through May 2022, a total of 1375 patients were screened and 1074 underwent randomization (429 patients to the amivantamab–lazertinib group, 429 to the osimertinib monotherapy group, and 216 to the lazertinib monotherapy group) (Fig. S2). A total of 1062 patients received at least one dose of trial treatment. Most of the patients were women, were Asian or White, and had never smoked, which is generally representative of the population of patients with *EGFR*-mutated NSCLC (Table S1). However, Blacks were underrepresented. The characteristics of the patients at baseline were well balanced among the groups (Table 1 and Table S2).

At a median follow-up of 22.0 months, the median duration of treatment was 18.5 months (range, 0.2 to 31.4) in the amivantamab–lazertinib group and 18.0 months (range, 0.2 to 32.7) in the osimertinib group. At the data-cutoff date, the assigned treatment was still being administered to 230 of 421 patients (55%) in the amivantamab–lazertinib group and to 213 of 428 (50%) in the osimertinib group. The most common reasons for treatment discontinuation of amivantamab–lazertinib combination therapy as compared with osimertinib monotherapy were progressive disease (in 86 patients [20%] and 154 patients [36%], respectively) and adverse events (in 86 [20%] and 50 [12%]). Among patients with disease progression who discontinued their randomly assigned treatment, 67% in the amivantamab–lazertinib group and 73% in the osimertinib group started a first subsequent therapy (Table S3).

EFFICACY

The median progression-free survival, as assessed on the basis of blinded independent central review, was 23.7 months (95% confidence interval [CI], 19.1 to 27.7) in the amivantamab–lazertinib group, as compared with 16.6 months (95% CI, 14.8 to 18.5) in the osimertinib group (Fig. 1A and Table 2). Progression-free survival was significantly longer in the amivantamab–lazertinib group than in the osimertinib group (hazard ratio for disease progression or death, 0.70; 95% CI, 0.58 to 0.85; P<0.001). The percentage of patients who were alive and free from disease progression was 60% (95% CI, 55 to 64) at 18 months and 48% (95% CI, 42 to 54) at 24 months in the amivantamab–lazertinib group and was 48% (95% CI, 43 to 53) at 18 months and 34% (95% CI, 28 to 39) at 24 months in the osimertinib group. The median progression-free survival in the lazertinib group was 18.5 months (95% CI, 14.8 to 20.1) (Fig. 1B). Comparison between the amivantamab–lazertinib and lazertinib groups to evaluate the contribution of amivantamab therapy is presented in Table S4.

Estimates of progression-free survival with amivantamab–lazertinib as compared with osimertinib in all the prespecified subgroups are shown in Figure 1C, including in subgroups defined according to *EGFR* mutation type (Fig. S3), Asian race (Fig. S4), and history of brain metastases (Fig. S5). Since serial imaging of the head was performed in this trial, we conducted a post hoc sensitivity analysis with censoring of first events of disease progression involving only the CNS. The median extracranial progression–free survival was 27.5 months (95% CI, 22.1 to could not be estimated) in the amivantamab–lazertinib group and 18.4 months (95% CI, 16.5 to 20.2) in the osimertinib group (Fig. S6).

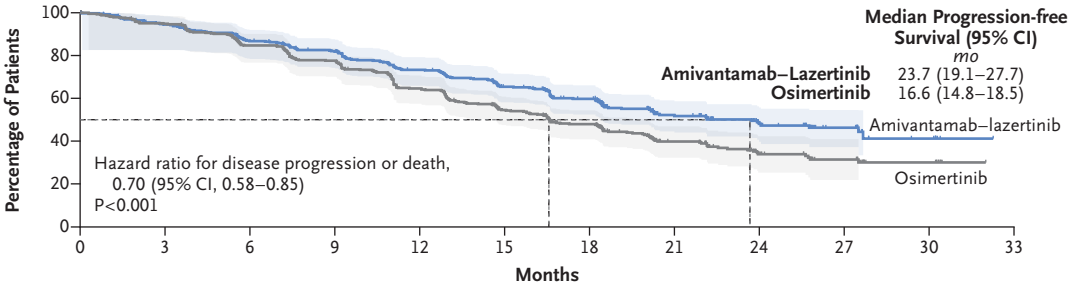
At the time of the interim overall survival analysis, the percentage of patients who were alive was 82% (95% CI, 78 to 85) at 18 months and 74% (95% CI, 69 to 78) at 24 months in the amivantamab–lazertinib group and was 79% (95% CI,

Table 1. Demographic and Baseline Disease Characteristics of the Patients.*

Characteristic	Amivantamab–Lazertinib (N = 429)	Osimertinib (N = 429)
Age		
Median (range) — yr	64 (25–88)	63 (28–88)
Distribution — no. (%)		
<65 yr	235 (55)	237 (55)
65 to <75 yr	143 (33)	139 (32)
≥75 yr	51 (12)	53 (12)
Female sex — no. (%)	275 (64)	251 (59)
Race or ethnic group — no. (%)†		
Asian	250 (58)	251 (59)
White	164 (38)	165 (38)
American Indian or Alaska Native	7 (2)	7 (2)
Black	4 (1)	3 (1)
Native Hawaiian or Pacific Islander	1 (<1)	1 (<1)
Multiple	1 (<1)	1 (<1)
Unknown	2 (<1)	1 (<1)
Body weight		
Median (range) — kg	62.5 (32–118)	62 (35–109)
Distribution — no. (%)		
<80 kg	376 (88)	368 (86)
≥80 kg	53 (12)	61 (14)
ECOG performance-status score — no. (%)‡		
0	141 (33)	149 (35)
1	288 (67)	280 (65)
History of smoking — no. (%)		
No	299 (70)	295 (69)
Yes	130 (30)	134 (31)
Median time from initial diagnosis to randomization (range) — mo	1.5 (0.2–207.9)	1.4 (0.3–162.8)
Median time from diagnosis of metastatic disease to randomization (range) — mo	1.3 (0.2–24.1)	1.2 (0.1–11.7)
Histologic type — no. (%)		
Adenocarcinoma	417 (97)	415 (97)
Large-cell carcinoma	3 (1)	0
Squamous-cell carcinoma	6 (1)	5 (1)
Other§	2 (<1)	9 (2)
Not reported	1 (<1)	0
History of brain metastases — no. (%)	178 (41)	172 (40)
EGFR mutation — no. (%)¶		
Ex19del	258 (60)	257 (60)
L858R	172 (40)	172 (40)

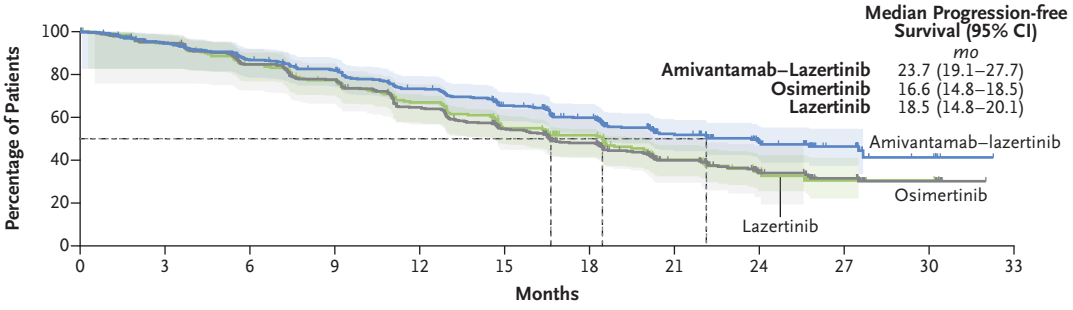
* Percentages may not total 100 because of rounding. EGFR denotes epidermal growth factor receptor, Ex19del exon 19 deletion, and L858R exon 21 codon p.Leu858Arg.
† Race or ethnic group was reported by the patient.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ Other histologic types included adenocarcinoma and squamous-cell carcinoma, lepidic adenocarcinoma, non–small-cell carcinoma, pleomorphic carcinoma, and unknown.
¶ One patient in the amivantamab–lazertinib group had both *EGFR* mutation types.

A Progression-free Survival in the Amivantamab–Lazertinib Group as Compared with the Osimertinib Group



No. at Risk												
Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

B Progression-free Survival in Amivantamab–Lazertinib Group as Compared with the Osimertinib and the Lazertinib Monotherapy Groups



No. at Risk												
Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0
Lazertinib	216	200	174	157	134	103	83	41	19	6	2	0

C Subgroup Analysis

Subgroup	Amivantamab–Lazertinib	Osimertinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. of patients		
All patients	192/429	252/429	0.70 (0.58–0.85)
Age			
<65 yr	94/235	153/237	0.50 (0.39–0.65)
≥65 yr	98/194	99/192	1.06 (0.80–1.41)
<75 yr	165/378	220/376	0.70 (0.57–0.85)
≥75 yr	27/51	32/53	0.77 (0.46–1.30)
Sex			
Male	112/275	140/251	0.70 (0.55–0.90)
Female	80/154	112/178	0.74 (0.55–0.98)
Race			
Asian	105/250	144/251	0.67 (0.52–0.86)
Non-Asian	85/177	108/177	0.75 (0.56–0.99)
Weight			
<80 kg	161/376	209/368	0.70 (0.57–0.86)
≥80 kg	31/53	43/61	0.77 (0.48–1.22)
ECOG performance-status score			
0	56/141	76/149	0.79 (0.56–1.12)
1	136/288	176/280	0.66 (0.52–0.82)
History of smoking			
Yes	67/130	79/134	0.78 (0.56–1.08)
No	125/299	173/295	0.67 (0.53–0.84)
History of brain metastases			
Yes	94/178	111/172	0.69 (0.53–0.92)
No	98/251	141/257	0.69 (0.53–0.89)
EGFR mutation			
Ex19del	101/257	142/257	0.65 (0.51–0.85)
L858R	90/171	110/172	0.78 (0.59–1.02)

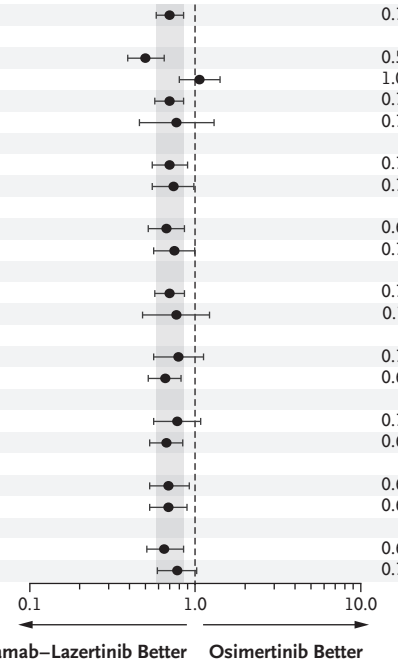


Figure 1 (facing page). Progression-free Survival, as Assessed by Blinded Independent Central Review.

Shown are Kaplan–Meier estimates of progression-free survival in the amivantamab–lazertinib group as compared with the osimertinib group, as assessed by blinded independent central review (Panel A). The analysis was conducted in the efficacy population, which was defined as all the patients who had undergone randomization. Progression-free survival in the lazertinib monotherapy group is shown in Panel B. In Panels A and B, dashed lines indicate the median progression-free survival in each group, tick marks indicate censored data, and shaded areas indicate 95% confidence intervals. In the subgroup analysis (Panel C), the shaded area indicates the 95% confidence interval for the overall hazard ratio among all the patients (primary end point). Except for the primary end point, 95% confidence intervals in the subgroup analysis were not adjusted for multiplicity, with the hazard ratios for progression or death obtained from an unstratified proportional-hazards model, and should not be used to infer definitive treatment effects. Race was reported by the patient. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. EGFR denotes epidermal growth factor receptor, Ex19del exon 19 deletion, and L858R exon 21 codon p.Leu858Arg.

75 to 83) at 18 months and 69% (95% CI, 64 to 74) at 24 months in the osimertinib group. The median overall survival could not be estimated in either group, with 214 total deaths reported across the amivantamab–lazertinib and osimertinib groups of the 390 deaths that had been anticipated during the trial period (Fig. 2 and Table 2). A total of 97 patients in the amivantamab–lazertinib group and 117 in the osimertinib group died, with 49 deaths and 82 deaths, respectively, being due to progressive disease. The hazard ratio for death was 0.80 (95% CI, 0.61 to 1.05).

The percentage of patients with an objective response was 86% (95% CI, 83 to 89) in the amivantamab–lazertinib group and 85% (95% CI, 81 to 88) in the osimertinib group (Fig. S7). Response was confirmed in 336 patients in the amivantamab–lazertinib group and in 314 in the osimertinib group. Among patients with a confirmed response, the median duration of response was 25.8 months (95% CI, 20.1 to could not be estimated) in the amivantamab–lazertinib group and 16.8 months (95% CI, 14.8 to 18.5) in the osimertinib group (Fig. S8 and Table S5). The time to treatment discontinuation, the time to subsequent therapy, and progression-free survival after the first subsequent therapy are shown in Figures S9, S10, and S11, respectively.

SAFETY

The safety population included 421 patients in the amivantamab–lazertinib group, 428 in the osimertinib group, and 213 in the lazertinib group. Most patients in the trial had at least one adverse event (Table 3 and Table S6). Grade 3 or higher adverse events were reported in 75% of the patients treated with amivantamab–lazertinib and in 43% of those treated with osimertinib, with paronychia and rash being the most common events. Serious adverse events were reported in 49% of the patients treated with amivantamab–lazertinib and in 33% of those treated with osimertinib (Table S7).

Infusion-related reactions occurred in 63% of the patients treated with amivantamab–lazertinib (Table 3), with the majority of events occurring on cycle 1 day 1. Venous thromboembolic adverse events were reported in 37% of the patients in the amivantamab–lazertinib group and in 9% of those in the osimertinib group, with pulmonary embolism and deep-vein thrombosis being the most common events (Tables S8 and S9). At baseline, 5% of all the patients across both these trial groups received anticoagulation treatment. At the time of the first venous thromboembolic adverse event, few patients (1% of the patients in the amivantamab–lazertinib group and none of those in the osimertinib group) were receiving anticoagulation treatment. Among the venous thromboembolic adverse events, 62% in the amivantamab–lazertinib group, as compared with 33% in the osimertinib group, occurred in the first 4 months of treatment. For patients in whom anticoagulation was initiated after the onset of a venous thromboembolic adverse event, bleeding events occurred in 8% of those in the amivantamab–lazertinib group and in 3% of those in the osimertinib group, and recurrent venous thromboembolic adverse events occurred in 2% of those in the amivantamab–lazertinib group and in none of the patients in the osimertinib group. Interstitial lung disease or pneumonitis was reported in 3% of the patients in each of these two groups, with grade 3 or higher events occurring in 1% in each group.

In the amivantamab–lazertinib group, adverse events leading to a dose interruption of any trial

Table 2. Key Efficacy End Points.*

End Point	Amivantamab–Lazertinib (N=429)	Osimertinib (N=429)	Treatment Effect (95% CI)	P Value
Progression-free survival				
Median (95% CI) — mo	23.7 (19.1–27.7)	16.6 (14.8–18.5)	0.70 (0.58–0.85)	<0.001
Percentage of patients alive and free from progression (95% CI)				
At 12 mo	73 (69–77)	65 (60–69)		
At 18 mo	60 (55–64)	48 (43–53)		
At 24 mo	48 (42–54)	34 (28–39)		
Overall survival				
Median (95% CI) — mo	NE	NE	0.80 (0.61–1.05)	—
Percentage of patients alive (95% CI)				
At 12 mo	90 (86–92)	88 (85–91)		
At 18 mo	82 (78–85)	79 (75–83)		
At 24 mo	74 (69–78)	69 (64–74)		
Objective response (95% CI) — %†	86 (83–89)	85 (81–88)	1.15 (0.78–1.70)	—
Median duration of response (95% CI) — mo‡	25.8 (20.1–NE)	16.8 (14.8–18.5)	—	—

* The efficacy population included all the patients who had undergone randomization. Progression-free survival (the primary end point) was assessed by blinded independent central review, and the treatment effect is shown as a hazard ratio for progression or death. In the analysis of overall survival, the treatment effect is shown as a hazard ratio for death. NE denotes could not be estimated.

† Objective response (defined as a complete or partial response) was assessed by blinded independent central review. Included in the analysis were 421 patients in the amivantamab–lazertinib group and 414 patients in the osimertinib group who had measurable disease at baseline. In the analysis of objective response, the treatment effect is shown as an odds ratio, which was calculated from a logistic-regression model with stratification according to *EGFR* mutation type, Asian race, and history of brain metastasis. The widths of the 95% confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

‡ The duration of response was assessed by blinded independent central review among 336 patients in the amivantamab–lazertinib group and 314 in the osimertinib group who had a confirmed response.

agent were reported in 350 patients (83%), leading to any dose reduction in 249 patients (59%), and leading to any discontinuation of treatment in 147 (35%); the corresponding numbers in the osimertinib group were 165 (39%), 23 (5%), and 58 (14%) (Table 3). The most common adverse events leading to the discontinuation of any trial agent were infusion-related reactions and paronychia (Table S10). A total of 10% of the patients in the amivantamab–lazertinib group and 3% of those in the osimertinib group discontinued all trial agents owing to treatment-related adverse events. Data on treatment-related adverse events are presented in Table S11.

Adverse events leading to death occurred in 34 patients (8%) in the amivantamab–lazertinib group and in 31 (7%) in the osimertinib group (Table S12). Cardiopulmonary-, cerebrovascular-, and infection-related deaths predominated in these two groups.

DISCUSSION

Although most patients with *EGFR*-mutated advanced NSCLC have an initial response to treatment with third-generation EGFR-TKIs, real-world survival estimates show that only 19% of patients are alive after 5 years.[33] There is a continuous need to improve clinical outcomes with first-line treatment beyond those seen with EGFR-TKI monotherapy, given that 25% of patients die before receiving second-line therapy.[34,35]

In the MARIPOSA trial, first-line treatment with amivantamab–lazertinib significantly prolonged progression-free survival as compared with osimertinib monotherapy (hazard ratio for disease progression or death, 0.70; P<0.001). The progression-free survival curves separated at 6 months and widened over time, according to the landmark analyses at 12, 18, and 24 months. With regard to progression-free survival, a benefit with ami-

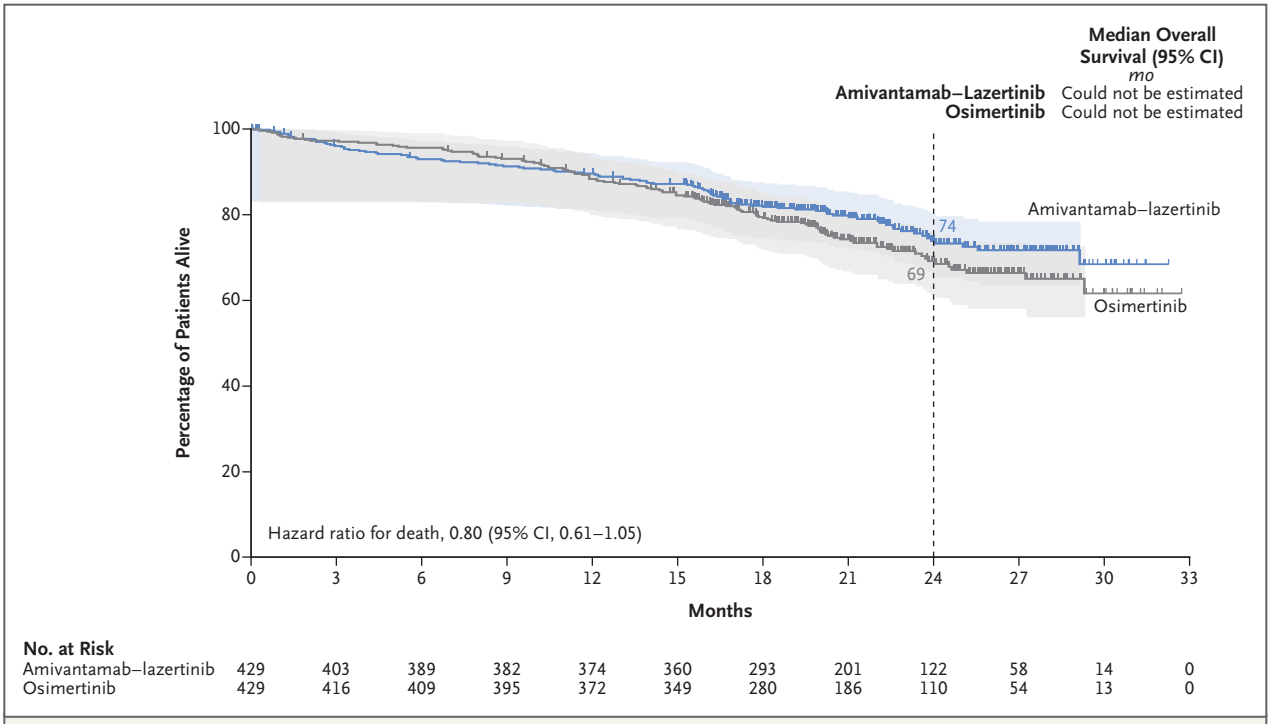


Figure 2. Overall Survival.

Shown is a Kaplan–Meier estimate of overall survival in an interim analysis. The analysis was conducted in the efficacy population. Tick marks indicate censored data, and shaded areas indicate 95% confidence intervals.

vantamab–lazertinib was also observed across key prespecified subgroups, such as those defined according to a history of brain metastases. In this trial, serial imaging of the head was performed in all the patients, which allowed for the robust evaluation of the treatment effect on intracranial outcomes and identified CNS metastases more frequently than if such imaging were not required. Therefore, cross-trial comparisons of progression-free survival estimates between the MARIPOSA trial and previous trials that did not require serial imaging of the head are not informative.

The scientific rationale for combining amivantamab with lazertinib was to proactively address mechanisms of resistance to osimertinib.[10-12] This rationale was based on findings regarding osimertinib that showed that activity against the leading cause of resistance to first-generation EGFR-TKIs (T790M mutation) was associated with improved progression-free survival over these agents.[7] Treatment with amivantamab–lazertinib offers the added benefit of preserving chemotherapy for use in later lines of therapy.

The number of deaths in our trial was inadequate to provide robust conclusions about overall survival. The analysis showed a hazard ratio for death of 0.80 in favor of the combination therapy, but the result was not significant. Longer follow-up is needed to detect whether there is an overall survival benefit with amivantamab–lazertinib.

Safety data regarding amivantamab–lazertinib were consistent with previous reports from phase 1–2 studies.[29-31,36] We found a high incidence of EGFR- and MET-related adverse events in the amivantamab–lazertinib group, except for diarrhea, which was more frequent in the osimertinib group. Most adverse events were of grade 1 or 2. The discontinuation of all agents due to treatment-related adverse events in the amivantamab–lazertinib group was infrequent, which suggests that most patients can continue receiving treatment.

The incidence of venous thromboembolic adverse events was higher with amivantamab–lazertinib than with osimertinib. However, the incidence of grade 4 or 5 events and the percentages of patients who discontinued treatment

Table 3. Adverse Events.*

Event	Amivantamab–Lazertinib (N=421)		Osimertinib (N=428)	
	All	Grade ≥3	All	Grade ≥3
	number of patients (percent)			
Any event	421 (100)	316 (75)	425 (99)	183 (43)
Any serious event	205 (49)		143 (33)	
Any event resulting in death		34 (8)		31 (7)
Event leading to interruption of any trial agent	350 (83)		165 (39)	
Event leading to dose reduction of any trial agent	249 (59)		23 (5)	
Event leading to discontinuation of any trial agent	147 (35)		58 (14)	
Adverse events reported in ≥15% of the patients in either group†				
Paronychia	288 (68)	46 (11)	121 (28)	2 (<1)
Infusion-related reaction	265 (63)	27 (6)	0	0
Rash	260 (62)	65 (15)	131 (31)	3 (1)
Hypoalbuminemia	204 (48)	22 (5)	26 (6)	0
Increased alanine aminotransferase	152 (36)	21 (5)	57 (13)	8 (2)
Peripheral edema	150 (36)	8 (2)	24 (6)	0
Constipation	123 (29)	0	55 (13)	0
Diarrhea	123 (29)	9 (2)	190 (44)	3 (1)
Dermatitis acneiform	122 (29)	35 (8)	55 (13)	0
Stomatitis	122 (29)	5 (1)	90 (21)	1 (<1)
Increased aspartate aminotransferase	121 (29)	14 (3)	58 (14)	5 (1)
Covid-19	111 (26)	8 (2)	103 (24)	9 (2)
Decreased appetite	103 (24)	4 (1)	76 (18)	6 (1)
Pruritus	99 (24)	2 (<1)	73 (17)	1 (<1)
Anemia	96 (23)	16 (4)	91 (21)	7 (2)
Nausea	90 (21)	5 (1)	58 (14)	1 (<1)
Hypocalcemia	88 (21)	9 (2)	35 (8)	0
Asthenia	78 (19)	12 (3)	46 (11)	4 (1)
Pulmonary embolism	73 (17)	35 (8)	20 (5)	10 (2)
Fatigue	70 (17)	6 (1)	42 (10)	4 (1)
Muscle spasms	70 (17)	2 (<1)	32 (7)	0
Dry skin	67 (16)	1 (<1)	60 (14)	1 (<1)
Thrombocytopenia	66 (16)	1 (<1)	84 (20)	5 (1)
Cough	65 (15)	0	88 (21)	0
Pain in extremity	64 (15)	1 (<1)	22 (5)	0
Dyspnea	51 (12)	6 (1)	68 (16)	17 (4)
Leukopenia	26 (6)	1 (<1)	66 (15)	0

* The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment. Adverse events were coded according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 25.1. Covid-19 denotes coronavirus disease 2019.

† Events in this category are listed according to decreasing incidence in the amivantamab–lazertinib group.

were low and similar in the two groups. Most venous thromboembolic adverse events in the amivantamab–lazertinib group occurred during the first 4 months of treatment. One possible explanation could be a transitory prothrombotic state caused by a mechanism of rapid tumor-cell death by amivantamab–lazertinib. This hypothesis is supported by the fact that the risk occurs early and that having a tumor response was previously identified as a risk factor.[37] The vast majority of patients were not receiving anticoagulation at the time of venous thromboembolism. Among patients in whom anticoagulation was initiated after the onset of a venous thromboembolic adverse event, the incidence of recurrent events and bleeding remained low in both groups. In ongoing trials of amivantamab–lazertinib (PALOMA-3[38] and COCOON [ClinicalTrials.gov number, NCT06120140]), prophylactic anticoagulation is now recommended for the first 4 months of treatment.

Key strengths of our trial include the blinded evaluation of two third-generation EGFR-TKIs, which showed a similarity in progression-free survival between the osimertinib group and the lazertinib group and established the contribution of the components in the combination treatment. A comparison of lazertinib with osimertinib will be informative.

In this trial, we found that progression-free survival was significantly improved with amivantamab–lazertinib as compared with osimertinib as first-line treatment for *EGFR*-mutated advanced NSCLC.

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APPENDIX

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