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ORIGINAL ARTICLE

Amivantamab plus chemotherapy with and without lazertinib in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study☆

A. Passaro[1*†], J. Wang[2†], Y. Wang[3], S.-H. Lee[4], B. Melosky[5], J.-Y. Shih[6], J. Wang[7], K. Azuma[8], O. Juan-Vidal[9], M. Cobo[10], E. Felip[11], N. Girard[12,13], A. B. Cortot[14], R. Califano[15], F. Cappuzzo[16], S. Owen[17], S. Popat[18], J.-L. Tan[19], J. Salinas[20], P. Tomasini[21], R. D. Gentzler[22], W. N. William, Jr.[23], K. L. Reckamp[24], T. Takahashi[25], S. Ganguly[26], D. M. Kowalski[27], A. Bearz[28], M. MacKean[29], P. Barala[30], A. B. Bourla[31], A. Girvin[30], J. Greger[30], D. Millington[32], M. Withelder[30], J. Xie[31], T. Sun[31], S. Shah[30], B. Diorio[31], R. E. Knoblauch[30], J. M. Bauml[30], R. G. Campelo[33‡] & B. C. Cho[34‡], for the MARIPOSA-2 Investigators[§]

[1]Division of Thoracic Oncology, European Institute of Oncology, IRCCS, Milan, Italy; [2]Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [3]Department of Thoracic Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]British Columbia Cancer Agency, Vancouver, Canada; [6]Department of Internal Medicine, National Taiwan University Hospital, Taipei City, Taiwan; [7]Fudan University Shanghai Cancer Center, Shanghai, China; [8]Kurume University School of Medicine, Kurume, Japan; [9]Hospital Universitari i Politécnic La Fe, Valencia, Spain; [10]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; [11]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France; [13]Paris Saclay University, UVSQ, Versailles, France; [14]University of Lille, CHU Lille, CNRS, Inserm, Institut Pasteur de Lille, UMR9020—UMR1277—Canther—Cancer Heterogeneity, Plasticity and Resistance to Therapies, F-59000 Lille, France; [15]Department of Medical Oncology, Christie NHS Foundation Trust and Division of Cancer Sciences, The University of Manchester, Manchester, UK; [16]IRCCS Regina Elena National Cancer Institute, Rome, Italy; [17]Department of Medical Oncology, McGill University Health Centre, Montreal, Quebec, Canada; [18]Royal Marsden Hospital NHS Foundation Trust and The Institute of Cancer Research, London, UK; [19]Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [20]Centro de Especialidades Medicas Ambulatorias e Investigación Clínica, Córdoba, Argentina; [21]Multidisciplinary Oncology and Therapeutic Innovations Department, Assistance Publique—Hôpitaux de Marseille, Aix-Marseille University, Marseille, France; [22]Hematology/Oncology, University of Virginia Cancer Center, Charlottesville, VA, USA; [23]Centro Oncológico BP, Beneficência Portuguesa de São Paulo, and Grupo Oncoclínicas, São Paulo, Brazil; [24]Cedars-Sinai Medical Center, Los Angeles, USA; [25]Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi, Japan; [26]Tata Medical Center, Kolkata, India; [27]Department of Lung Cancer and Thoracic Tumours, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [28]Medical Oncology, Centro di Riferimento Oncologico—CRO, Aviano, Italy; [29]Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK; [30]Janssen Research & Development, Spring House, PA, USA; [31]Janssen Research & Development, Raritan, NJ, USA; [32]Janssen Research & Development, San Diego, CA, USA; [33]University Hospital A Coruña, A Coruña, Spain; [34]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

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Background: Amivantamab plus carboplatin—pemetrexed (chemotherapy) with and without lazertinib demonstrated antitumor activity in patients with refractory epidermal growth factor receptor (*EGFR*)-mutated advanced non-small-cell lung cancer (NSCLC) in phase I studies. These combinations were evaluated in a global phase III trial.

Patients and methods: A total of 657 patients with *EGFR*-mutated (exon 19 deletions or L858R) locally advanced or metastatic NSCLC after disease progression on osimertinib were randomized 2 : 2 : 1 to receive amivantamab—lazertinib—chemotherapy, chemotherapy, or amivantamab—chemotherapy. The dual primary endpoints were progression-free survival (PFS) of amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy versus chemotherapy. During the study, hematologic toxicities observed in the amivantamab—lazertinib—chemotherapy arm necessitated a regimen change to start lazertinib after carboplatin completion.

Results: All baseline characteristics were well balanced across the three arms, including by history of brain metastases and prior brain radiation. PFS was significantly longer for amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy versus chemotherapy [hazard ratio (HR) for disease progression or death 0.48 and 0.44, respectively; $P < 0.001$ for both; median of 6.3 and 8.3 versus 4.2 months, respectively]. Consistent PFS results were seen by investigator assessment (HR for disease progression or death 0.41 and 0.38 for amivantamab

*Correspondence to: Dr Antonio Passaro, Division of Thoracic Oncology, European Institute of Oncology-IEO, Via G. Ripamonti, 435-20141 Milan, Italy. Tel: +39-0257489482

E-mail: antonio.passaro@ieo.it (A. Passaro).

†These authors contributed equally.

‡These authors contributed equally.

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§A complete list of the investigators in the MARIPOSA-2 trial is provided in the Supplementary Material.

—chemotherapy and amivantamab—lazertinib—chemotherapy, respectively; $P < 0.001$ for both; median of 8.2 and 8.3 versus 4.2 months, respectively). Objective response rate was significantly higher for amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy versus chemotherapy (64% and 63% versus 36%, respectively; $P < 0.001$ for both). Median intracranial PFS was 12.5 and 12.8 versus 8.3 months for amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy versus chemotherapy (HR for intracranial disease progression or death 0.55 and 0.58, respectively). Predominant adverse events (AEs) in the amivantamab-containing regimens were hematologic, *EGFR*-, and *MET*-related toxicities. Amivantamab—chemotherapy had lower rates of hematologic AEs than amivantamab—lazertinib—chemotherapy.

Conclusions: Amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy improved PFS and intracranial PFS versus chemotherapy in a population with limited options after disease progression on osimertinib. Longer follow-up is needed for the modified amivantamab—lazertinib—chemotherapy regimen.

Key words: amivantamab, lazertinib, *EGFR*-mutated, NSCLC, post-osimertinib

INTRODUCTION

Mutations in the epidermal growth factor receptor (*EGFR*) gene are the most common actionable genomic alterations in non-small-cell lung cancer (NSCLC). Of *EGFR* mutations, 85%-90% are exon 19 deletions (Ex19del) and L858R substitution mutations.[1,2] The current first-line standard of care in *EGFR*-mutated NSCLC is the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib,[3,4] which improved progression-free survival (PFS) and overall survival versus first-generation TKIs.[5,6] Despite initial efficacy, nearly all patients treated with osimertinib develop resistance.[7] Mechanisms of resistance to osimertinib are diverse and polyclonal, with the most common being alterations in the *MET* gene (e.g. up to 51% by fluorescence *in situ* hybridization)[8] and *EGFR* pathways.[9-12] Guidelines recommend platinum-based chemotherapy as the next line of therapy,[13,14] with a historical median PFS of 4.4-5.5 months in patients with disease progression after TKI treatment.[15-18]

Amivantamab, an EGFR-MET bispecific antibody with immune cell—directing activity,[19-21] is approved for the treatment of patients with *EGFR* exon 20 insertion mutations whose disease progressed on or after platinum-based chemotherapy.[22] Amivantamab has multiple mechanisms of action, including ligand blocking, receptor degradation, and engagement of effector cells (natural killer cells, monocytes, and macrophages) via its optimized Fc domain.[19,20] Mechanistically, by binding extracellularly, amivantamab bypasses intracellular mutations (including those at the TKI catalytic domain), and its bispecific nature addresses *MET* as a mechanism of resistance. Clinically, amivantamab has shown activity against a wide range of activating and resistance mutations in *EGFR*-mutated NSCLC and in patients with *MET* exon 14 skip mutations.[23-26]

Lazertinib is a highly selective, central nervous system (CNS)—penetrant, third-generation TKI with demonstrated efficacy in activating *EGFR* mutations and T790M resistance.[27,28] Simultaneously targeting the extracellular and catalytic EGFR domains by combining amivantamab with lazertinib (amivantamab—lazertinib) has been shown to provide a synergistic benefit.[29,30] Amivantamab—lazertinib has demonstrated clinically meaningful activity in patients with *EGFR*-mutated NSCLC after disease progression on osimertinib.[31] Additionally, continuation of a CNS-penetrant, third-generation TKI, such as lazertinib, after disease progression on osimertinib has been thought to be important since brain metastasis is a frequent outcome for patients with *EGFR*-mutated NSCLC.[32]

The addition of carboplatin—pemetrexed (chemotherapy) to amivantamab or amivantamab plus lazertinib could address osimertinib-based resistance. In a phase I study, amivantamab—chemotherapy demonstrated an objective response rate of 44% in a safety population of 20 patients with advanced and refractory NSCLC.[33] In a separate phase I study, amivantamab—lazertinib—chemotherapy was evaluated in 20 patients with *EGFR*-mutated NSCLC whose disease had progressed on prior TKIs and showed an objective response rate of 50%.[34] The aforementioned results supported further evaluation.

MARIPOSA-2 is a global, randomized, phase III trial assessing the efficacy and safety of amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy versus chemotherapy in patients with *EGFR*-mutated advanced NSCLC whose disease had progressed on or after osimertinib monotherapy.

PATIENTS AND METHODS

Patients

MARIPOSA-2 (ClinicalTrials.gov identifier, NCT04988295) enrolled patients who were 18 years of age or older and had locally advanced or metastatic *EGFR*-mutated (Ex19del or L858R) NSCLC with disease progression on or after osimertinib monotherapy (as the most recent line of treatment). Patients with brain metastases were eligible provided intracranial disease was clinically stable, asymptomatic, and on stable doses of steroids; prior definitive treatment with radiation or surgery was not required. For additional criteria, see Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2023.10.117.

Trial oversight

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference on Harmonisation), applicable regulatory requirements, and the policy on bioethics and human biologic samples of

Janssen Pharmaceuticals (trial sponsor). Each patient (or legally acceptable representative) provided written consent for participation. Informed consent could be obtained remotely by telephone or video conferencing where permitted by local regulations.

MARIPOSA-2 was designed by the sponsor, who was responsible for the collection and analysis of the data and interpreted the trial data in collaboration with the authors. The first draft of the manuscript was written by the authors, with medical writing support funded by the sponsor and conducted in accordance with Good Publication Practice guidelines. All authors made the decision to publish and vouch for data completeness and accuracy, data analyses, and adherence to the clinical trial to the protocol. The protocol, amendments, and statistical analysis plan are available in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.10.117.

Trial design and treatment

Patients were randomly assigned in a 2 : 2 : 1 ratio to receive amivantamab—lazertinib—chemotherapy, chemotherapy alone, or amivantamab—chemotherapy in 21-day cycles (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.10.117). Amivantamab was administered intravenously at 1400 mg (1750 mg for body weight $\geq$80 kg) weekly for the first 4 weeks, and then 1750 mg (2100 mg for body weight $\geq$80 kg) every 3 weeks starting at cycle 3 (week 7). The first amivantamab infusion was split over 2 days, with 350 mg on cycle 1, day 1 and the remainder on cycle 1, day 2. Lazertinib was administered orally at 240 mg daily. Chemotherapy was administered intravenously at the beginning of every cycle, with pemetrexed at 500 mg/m^2 administered every cycle and carboplatin at area under the curve 5 for the first four cycles. Amivantamab, lazertinib, and pemetrexed treatments were to be continued until disease progression or lack of clinical benefit as deemed by the investigator. Treatment blinding was not possible due to differences in administration, premedication requirements, and safety profiles of the regimens. Randomization was stratified by osimertinib line of therapy (first or second), race (Asian or non-Asian), and history of brain metastasis (yes or no).

Originally, the MARIPOSA-2 study design included amivantamab—chemotherapy for the purposes of establishing contribution of components between amivantamab—lazertinib—chemotherapy and chemotherapy. In addition, there was a prespecified biomarker analysis with hypothesis testing, which was to be based upon next-generation sequencing (NGS). Emerging data did not validate the proposed NGS biomarker,[26,31] so the analysis plan needed to be updated. Due to emerging phase I data that demonstrated promising antitumor activity of amivantamab—chemotherapy,[33] the study was amended to allow dual hypothesis testing to independently assess amivantamab—chemotherapy versus chemotherapy. This decision was thus based on factors external to the MARIPOSA-2 study; no interim analysis of safety or efficacy was carried out before the implementation of the modification.

Based on reports of increased rates of venous thromboembolism (VTE) for amivantamab plus lazertinib, which were identified midway through the trial,[31,35] oral and subcutaneous anticoagulants (using either a direct oral anticoagulant or low-molecular-weight heparin, consistent with local guidelines) were recommended but not mandatory for patients receiving amivantamab—lazertinib—chemotherapy for the first 4 months of amivantamab—lazertinib treatment.

During the study, the independent data monitoring committee observed increased hematologic and gastrointestinal toxicities occurring within the first four cycles of the amivantamab—lazertinib—chemotherapy arm. The original dosing schedule for amivantamab—lazertinib—chemotherapy was modified to defer the start of lazertinib until after completion of carboplatin. Due to limited follow-up after the regimen change and to further describe the safety and efficacy of the modified regimen, a separate open-label, randomized extension cohort comparing the modified amivantamab—lazertinib—chemotherapy regimen versus amivantamab—chemotherapy is ongoing and will enroll an additional 90 patients (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.10.117). All amendments are described in the protocol.

Endpoints

The dual primary endpoints evaluated PFS as determined by blinded independent central review according to Response Evaluation Criteria in Solid Tumors version 1.1[36] for amivantamab—chemotherapy versus chemotherapy and amivantamab—lazertinib—chemotherapy versus chemotherapy. As per protocol, all patients in the amivantamab—lazertinib—chemotherapy arm, regardless of the dosing schedule, were compared to those receiving chemotherapy. Secondary endpoints included objective response rate, duration of response, overall survival, PFS after first subsequent therapy, symptomatic PFS, intracranial PFS, and safety. All endpoints are listed and defined in the protocol.

Trial assessments

Disease assessments occurred at baseline, at 6 ($+1$) weeks after randomization, then every 6 (±1) weeks for the first 12 months, and then every 12 (±1) weeks thereafter until disease progression was confirmed by blinded independent central review. Brain magnetic resonance imaging was carried out at baseline, 6 ($+1$) weeks, 12 (±1) weeks, and then every 12 (±1) weeks until intracranial disease progression confirmed by blinded independent central review. Baseline assessments were carried out within 28 days before randomization. Adverse events (AEs), vital signs, and laboratory tests were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Electrocardiograms were assessed at baseline.

Statistical analysis

The efficacy analysis included all randomly assigned patients on an intent-to-treat basis, while the safety analysis included all randomized patients who received at least one

dose of any study treatment. For PFS, it was estimated that 600 patients with 350 events in all three arms combined would provide approximately 83% and 93% power for amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy, respectively, versus chemotherapy to achieve a statistically significant difference for a hazard ratio (HR) of 0.65, with an overall two-sided α of 0.05. This sample size determination assumed a median PFS of 5.5 months for chemotherapy[15,16] and 8.5 months for amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy.

Multiplicity was adjusted using a graphical approach. For dual hypothesis testing, treatment effects of amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy were independently compared to chemotherapy based on a log-rank test stratified by line of therapy, history of brain metastases, and Asian race, with initial testing of PFS at a two-sided α of 0.03 and 0.02, respectively. If both were significant, based on the prespecified α recycling procedure, objective response rate was then evaluated at 0.0267 and 0.0233 for amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy, respectively, versus chemotherapy. If objective response rate was significant, overall survival was then evaluated for its first interim analysis via O'Brien Fleming α spending approach implemented by Lan—DeMets method. An interim overall survival analysis was planned at the time of primary analysis for PFS. Assuming PFS and objective response were significant for both amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy versus chemotherapy, then the interim analysis of overall survival would be evaluated at α of 0.000197 and 0.000138, respectively.

For PFS and overall survival, HRs and 95% confidence intervals (CIs) were calculated from a stratified Cox regression model with treatment as the sole explanatory variable, using the same stratification factors as for the log-rank test. Median and corresponding 95% CIs were estimated by the Kaplan—Meier method. Objective response was analyzed using a stratified logistic regression model with treatment as the explanatory variable.

Analyses of the additional secondary or other outcomes including the subgroup analyses, which were not part of the hypothesis testing in the study, are reported as point estimates and 95% CIs without adjusting for multiplicity. Additional statistical and multiplicity details are provided in the Supplementary Appendix, available at https://doi.org/10.1016/j.annonc.2023.10.117.

All data reported here are based on the primary analysis. The data cut-off date was 10 July 2023.

RESULTS

Patients and treatment

From December 2021 to April 2023, a total of 970 patients were screened and 657 patients were randomized (131 to amivantamab—chemotherapy, 263 to amivantamab—lazertinib—chemotherapy, and 263 to chemotherapy). One patient in the amivantamab—chemotherapy arm, none in the amivantamab—lazertinib—chemotherapy arm, and 20 in the chemotherapy arm did not receive treatment, leaving 636 (97%) patients who were treated (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2023.10.117). Demographics and baseline disease characteristics were well balanced across all three arms (Table 1). The percentage of patients with a history of brain metastases and the percentage of these who had received prior radiation treatment to the brain were also similar between arms. At a median follow-up of 8.7 months, the median treatment duration was 6.3 months (range 0-14.7 months) for amivantamab—chemotherapy, 5.8 months (range 0.1-18.6 months) for amivantamab—lazertinib—chemotherapy, and 3.7 months (range 0-15.9 months) for chemotherapy (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.10.117). The most common reason for treatment discontinuation (of all agents) was progressive disease, at 41 (32%), 68 (26%), and 152 (63%) patients in the amivantamab—chemotherapy, amivantamab—lazertinib—chemotherapy, and chemotherapy arms, respectively.

In the amivantamab—lazertinib—chemotherapy arm, 166 patients received lazertinib concurrently with all other agents and 97 received lazertinib after completion of carboplatin, with median follow-up of 11.5 and 5.4 months, respectively. As a result, the majority of patients receiving the modified amivantamab—lazertinib—chemotherapy regimen (lazertinib after completion of carboplatin) have had very limited treatment with lazertinib at the time of data cutoff. Data on efficacy and safety of the modified regimen will be presented in a future publication.

Efficacy

The median PFS by blinded independent central review was 6.3 months (95% CI 5.6-8.4 months) for patients treated with amivantamab—chemotherapy, 8.3 months (95% CI 6.8-9.1 months) with amivantamab—lazertinib—chemotherapy, and 4.2 months (95% CI 4.0-4.4 months) with chemotherapy (Figure 1A). PFS was significantly longer in the amivantamab—chemotherapy arm compared to the chemotherapy arm (HR for disease progression or death 0.48, 95% CI 0.36-0.64, $P < 0.001$) and in the amivantamab—lazertinib—chemotherapy arm compared to the chemotherapy arm (HR for disease progression or death 0.44, 95% CI 0.35-0.56, $P < 0.001$).

The median investigator-assessed PFS was 8.2 months (95% CI 6.8-10.9 months) for amivantamab—chemotherapy and 8.3 months (95% CI 7.1-9.9 months) for amivantamab—lazertinib—chemotherapy versus 4.2 months (95% CI 4.0-4.5 months) for chemotherapy, corresponding to HRs for disease progression or death of 0.41 (95% CI 0.30-0.54) and 0.38 (95% CI 0.30-0.48), respectively (Figure 1B and Supplementary Figure S4 and Table S2, available at https://doi.org/10.1016/j.annonc.2023.10.117).

The PFS benefit was consistent across predefined subgroups for amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy (Figure 2), including by

Table 1. Demographics and baseline disease characteristics

Characteristic	Chemotherapy (n = 263)	Amivantamab—chemotherapy (n = 131)	Amivantamab—lazertinib—chemotherapy (n = 263)
Age			
Median (range), years	62 (31-85)	62 (36-84)	61 (23-83)
Category, *n* (%)			
<65 years	166 (63)	79 (60)	163 (62)
≥65 years	97 (37)	52 (40)	100 (38)
Sex, *n* (%)			
Female	157 (60)	81 (62)	168 (64)
Male	106 (40)	50 (38)	95 (36)
Race, *n* (%)			
Asian	127 (48)	63 (48)	125 (48)
White	123 (47)	60 (46)	129 (49)
Other[a]	13 (5)	8 (6)	9 (3)
Region of enrollment, *n* (%)			
Asia[b]	126 (48)	67 (51)	131 (50)
Europe[c]	96 (37)	45 (34)	96 (37)
North America	22 (8)	13 (10)	21 (8)
South America	19 (7)	6 (5)	15 (6)
Body weight, kg			
Median (range)	63 (37-118)	63 (39-112)	64 (35-118)
Category, *n* (%)			
<80 kg	226 (86)	113 (86)	226 (86)
≥80 kg	37 (14)	18 (14)	37 (14)
ECOG performance status, *n* (%)			
0	101 (38)	55 (42)	92 (35)
1	162 (62)	76 (58)	171 (65)
History of smoking, *n* (%)			
No	168 (64)	90 (69)	175 (67)
Yes	95 (36)	41 (31)	87 (33)
Unknown	0	0	1 (0.4)
Time from metastatic diagnosis, median (range), months	21.0 (0.1-99.1)	23.0 (0.2-115.3)	21.5 (0.9-115.3)
Histologic type, *n* (%)			
Adenocarcinoma	260 (99)	130 (99)	260 (99)
Other[d]	3 (1)	1 (1)	3 (1)
History of brain metastases, *n* (%)	120 (46)	58 (44)	120 (46)
No prior brain radiation	61 of 120 (51)	24 of 58 (41)	56 of 120 (47)
Type of *EGFR* mutation, *n* (%)			
Exon 19 deletion	183 (70)	89 (68)	165 (63)
Exon 21 L858R	79 (30)	42 (32)	98 (37)
Previous osimertinib line of therapy,[e] *n* (%)			
Osimertinib as first line	181 (69)	97 (74)	185 (70)
Osimertinib as second line	82 (31)	34 (26)	77 (29)

Those with a history of smoking were defined as patients who used tobacco, cigarettes, cigars, or pipes.
ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.
[a]Other includes Black or African American, American Indian or Alaska Native, multiple, unknown, and not reported.
[b]Turkey counted as part of Asia.
[c]Russia counted as part of Europe.
[d]Other includes large cell carcinoma, squamous cell carcinoma, and other.
[e]One patient in the amivantamab—lazertinib—chemotherapy arm received osimertinib later than second line and is not included in the table.

history of brain metastases (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2023.10.117), osimertinib line of therapy (Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2023.10.117), and *EGFR* mutation type (Supplementary Figure S7, available at https://doi.org/10.1016/j.annonc.2023.10.117).

The objective response rate was 64% (95% CI 55%-72%) for amivantamab—chemotherapy, 63% (95% CI 57%-69%) for amivantamab—lazertinib—chemotherapy, and 36% (95% CI 30%-42%) for chemotherapy (Table 2; Supplementary Figure S8, available at https://doi.org/10.1016/j.annonc.2023.10.117), with significant improvements versus chemotherapy for amivantamab—chemotherapy (odds ratio 3.10, 95% CI 2.00-4.80, $P < 0.001$) and amivantamab—lazertinib—chemotherapy (odds ratio 2.97, 95% CI 2.08-4.24, $P < 0.001$). Among confirmed responders, median duration of response was 6.9 months (95% CI 5.5 months-not estimable) for amivantamab—chemotherapy, 9.4 months (95% CI 6.9 months-not estimable) for amivantamab—lazertinib—chemotherapy, and 5.6 months (95% CI 4.2-9.6 months) for chemotherapy.

At the time of this first interim overall survival analysis, the HRs for death were 0.77 (95% CI 0.49-1.21) for amivantamab—chemotherapy versus chemotherapy and 0.96 (95% CI 0.67-1.35) for amivantamab—lazertinib—chemotherapy versus chemotherapy (Supplementary Figure S9, available at https://doi.org/10.1016/j.annonc.2023.10.117).

Median intracranial PFS by blinded independent central review was 12.5 months (95% CI 10.8 months-not estimable) for amivantamab—chemotherapy, 12.8 months

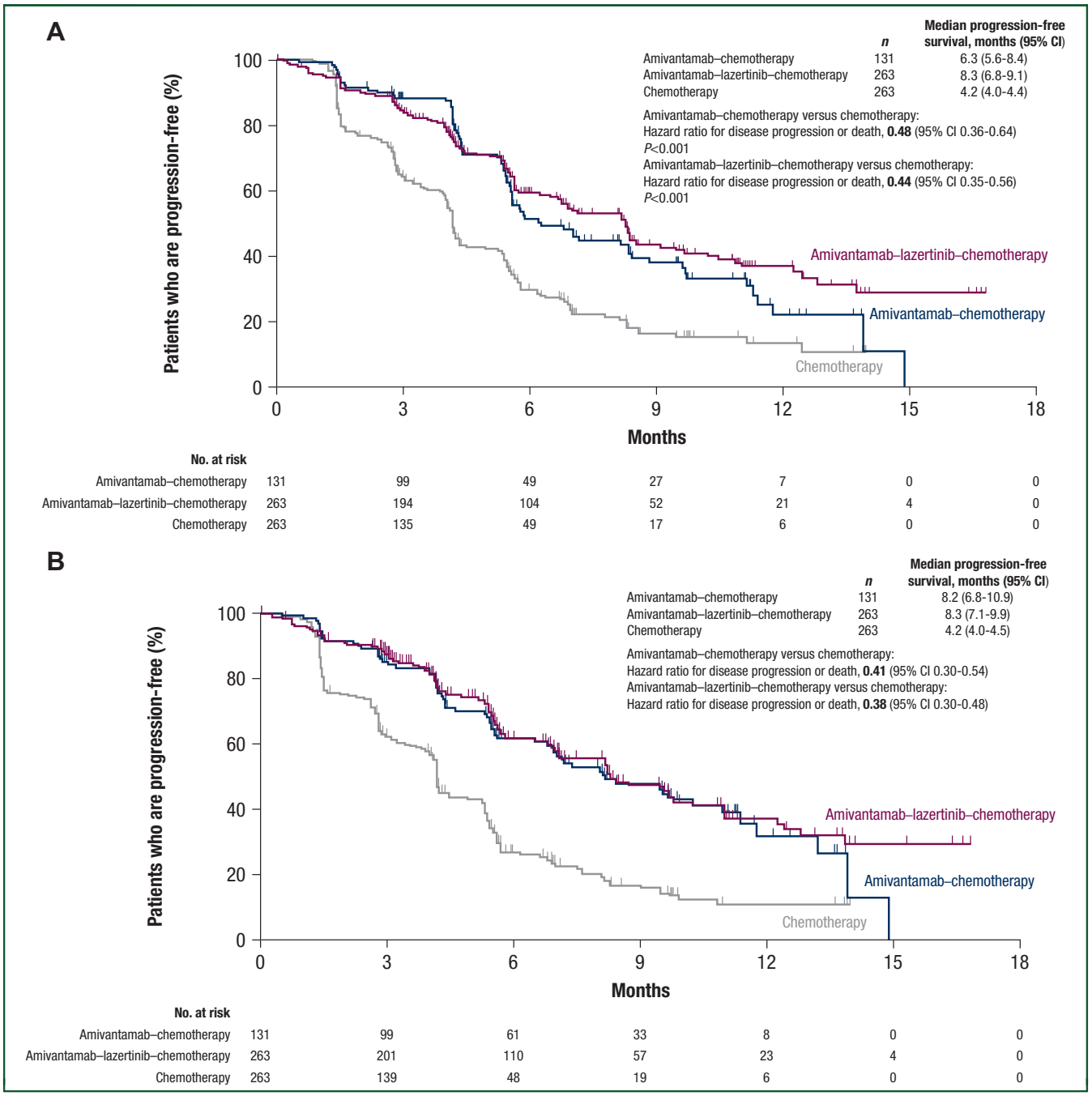
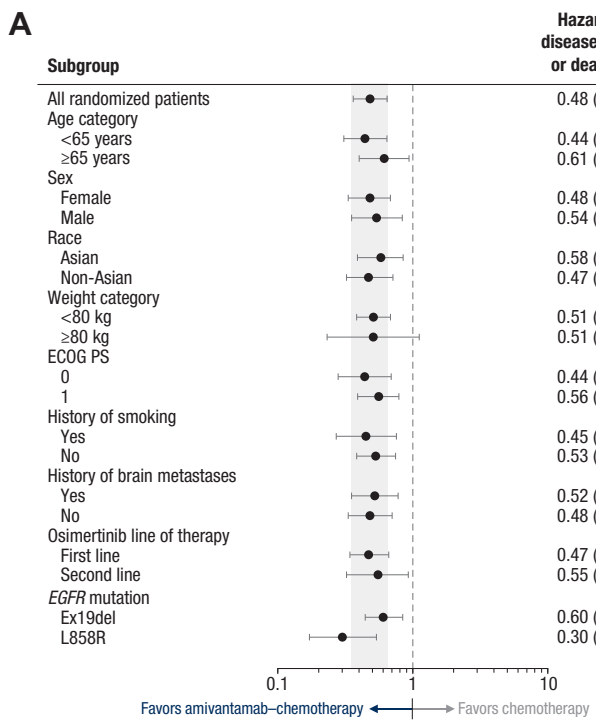


Figure 1. Progression-free survival by blinded independent central review and by investigator.
Shown are Kaplan—Meier estimates of progression-free survival assessed by blinded independent central review (A) and investigator assessment (B). The efficacy analysis set included all randomized patients. Tick marks indicate censoring of data. CI, confidence interval.

(95% CI 11.1-14.3 months) for amivantamab—lazertinib—chemotherapy, and 8.3 months (95% CI 7.3-11.3 months) for chemotherapy (Figure 3A; Table 2). The HR for intracranial disease progression or death was 0.55 (95% CI 0.38-0.79) for amivantamab—chemotherapy versus chemotherapy and 0.58 (95% CI 0.44-0.78) for amivantamab—lazertinib—chemotherapy versus chemotherapy. A sensitivity analysis was carried out among patients with a history of brain metastases and no prior brain radiotherapy (see Table 1 for subgroup). The intracranial PFS benefit of amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy versus chemotherapy was consistent with the overall population (Figure 3B). The median intracranial PFS was not estimable for amivantamab—chemotherapy (95% CI 5.6 months-not estimable) and 11.1 months for amivantamab—lazertinib—chemotherapy (95% CI 7.0-13.5 months) versus 6.3 months (95% CI 3.5-8.5 months) for chemotherapy, which corresponded to HRs for intracranial disease progression or death of 0.36 (95% CI 0.16-0.84) and 0.44 (95% CI 0.25-0.79), respectively.



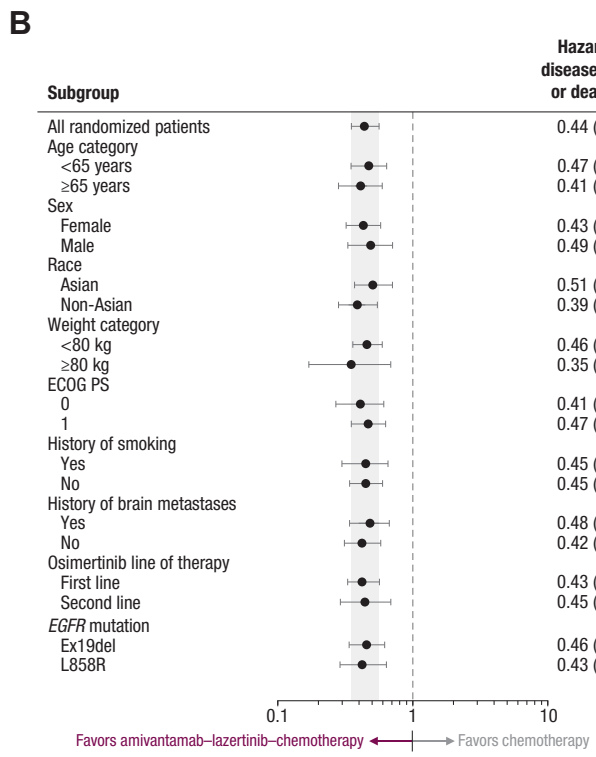


Figure 2. Progression-free survival by blinded independent central review of patient subgroups.
Shown are forest plots of progression-free survival in patient subgroups assessed by blinded independent central review for amivantamab—chemotherapy versus chemotherapy (A) and for amivantamab—lazertinib—chemotherapy versus chemotherapy (B). The efficacy analysis set included all randomized patients. The shaded areas indicate the 95% CI for the overall hazard ratio (all patients). CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety

AEs of grade 3 or higher, mainly due to hematologic toxicities, were reported by 72% of patients treated with amivantamab—chemotherapy, 92% with amivantamab—lazertinib—chemotherapy, and 48% with chemotherapy (Table 3). The most common grade 3 or higher AEs (10% or higher in any arm) included neutropenia, thrombocytopenia, anemia, and leukopenia. Analysis of mean neutrophil and platelet counts over time revealed transient decreases during cycle 1 followed by recovery by cycle 2 day 1 and

Table 2. Key efficacy endpoints by blinded independent central review

Endpoint	Chemotherapy (n = 263)	Amivantamab—chemotherapy (n = 131)	Amivantamab—lazertinib—chemotherapy (n = 263)
Progression-free survival			
No. of months, median (95% CI)	4.2 (4.0-4.4)	6.3 (5.6-8.4)	8.3 (6.8-9.1)
% of patients progression-free at 6 months (95% CI)	30 (23-36)	51 (41-60)	59 (52-65)
% of patients progression-free at 12 months (95% CI)	13 (8-20)	22 (12-34)	37 (29-45)
Objective response rate,[a] % (95% CI)	36 (30-42)	64 (55-72)	63 (57-69)
Duration of response[a]			
No. of months, median (95% CI)[b]	5.6 (4.2-9.6)	6.9 (5.5-NE)	9.4 (6.9-NE)
Intracranial progression-free survival			
No. of months, median (95% CI)	8.3 (7.3-11.3)	12.5 (10.8-NE)	12.8 (11.1-14.3)
% of patients progression-free at 6 months (95% CI)	66 (59-72)	78 (69-85)	79 (74-84)
% of patients progression-free at 12 months (95% CI)	34 (23-45)	50 (35-64)	54 (45-63)

Efficacy analysis included all randomly assigned patients.
CI, confidence interval; NE, not estimable.
[a]No. of patients with measurable disease at baseline by blinded independent central review was 260 for chemotherapy, 130 for amivantamab—chemotherapy, and 259 for amivantamab—lazertinib—chemotherapy.
[b]Duration of response among confirmed responders.

stabilization thereafter (Supplementary Figure S10, available at https://doi.org/10.1016/j.annonc.2023.10.117). The incidence of febrile neutropenia was 2%, 8%, and 2% for the amivantamab—chemotherapy, amivantamab—lazertinib—chemotherapy, and chemotherapy arms, respectively. Grade 3 or 4 bleeding events were seen in 1% of patients treated with amivantamab—chemotherapy, 3% with amivantamab—lazertinib—chemotherapy, and 0% with chemotherapy. Serious treatment-emergent AEs were observed in 32% of patients treated with amivantamab—chemotherapy, 52% with amivantamab—lazertinib—chemotherapy, and 20% with chemotherapy. The most common serious treatment-emergent AEs (5% or higher in any arm) were thrombocytopenia, neutropenia, and febrile neutropenia (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.10.117).

Infusion-related reactions occurred in 58% and 56% of patients on amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy, respectively (Table 3). VTE occurred in 10%, 22%, and 5% of patients in the amivantamab—chemotherapy, amivantamab—lazertinib—chemotherapy, and chemotherapy arms, respectively (Table 3; Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.10.117). At the time of first VTE, very few patients were receiving anticoagulation (0% amivantamab—chemotherapy, 2% amivantamab—lazertinib—chemotherapy, 1% for chemotherapy). Treatment-related AEs are provided in Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2023.10.117.

Dose interruptions, reductions, and discontinuations due to AEs occurred in 84 (65%), 53 (41%), and 24 (18%) patients treated with amivantamab—chemotherapy, 202 (77%), 171 (65%), and 90 (34%) with amivantamab—lazertinib—chemotherapy, and 81 (33%), 37 (15%), and 9 (4%) with chemotherapy (Table 3). The most common reasons for interruptions, reductions, and discontinuations were hematologic toxicities (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2023.10.117). Treatment-related AEs leading to discontinuation of all study agents were observed in 11 (8%), 25 (10%), and 6 (2%) patients receiving amivantamab—chemotherapy, amivantamab—lazertinib—chemotherapy, and chemotherapy, respectively.

Death within 30 days of the last dose occurred in 5%, 10%, and 3% of patients treated with amivantamab—chemotherapy, amivantamab—lazertinib—chemotherapy, and chemotherapy, respectively (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.10.117; all grade 5 AEs in Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2023.10.117). Treatment-related AEs leading to death were infrequent in all arms; there were two (2%) deaths in the amivantamab—chemotherapy arm, four (2%) in the amivantamab—lazertinib—chemotherapy arm, and one (0.4%) in the chemotherapy arm. No clear pattern of specific AEs leading to death was detected.

DISCUSSION

Amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy significantly improved PFS versus chemotherapy, with a 52% and 56% lower risk of disease progression or death, respectively. Early separation of curves was observed between both amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy versus chemotherapy. The PFS benefit was consistent across predefined subgroups. Mechanistically, amivantamab has shown efficacy against *EGFR* C797S, *MET* amplification, and other *EGFR*- and/or *MET*-based alterations after osimertinib.[30] Chemotherapy provides activity against other resistance mechanisms that are *EGFR*- and *MET*-independent. Together, this combination provides broad coverage of the diverse and polyclonal tumor resistance arising after disease progression on osimertinib.

It is notable that amivantamab—chemotherapy demonstrated similar intracranial PFS advantages over chemotherapy as amivantamab—lazertinib—chemotherapy. Amivantamab is a large molecule and was not expected to readily cross the blood—brain barrier. This was one of the key reasons for the addition of lazertinib, a known CNS-

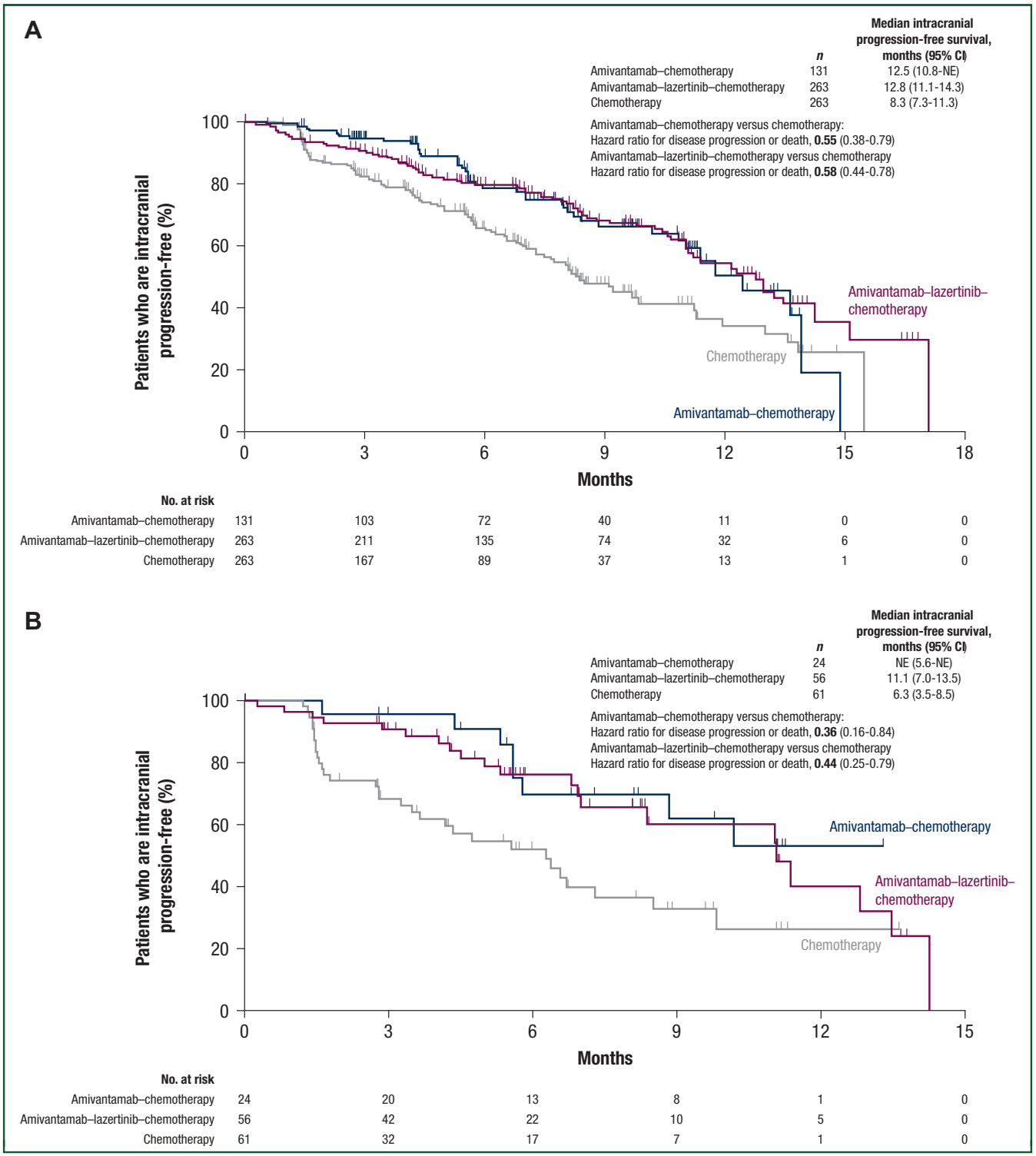


Figure 3. Intracranial progression-free survival.
Shown are Kaplan—Meier estimates of intracranial progression-free survival assessed by blinded independent central review in all randomized patients (A) and in patients with a history of brain metastases and no prior radiotherapy (B). The efficacy analysis set included all randomized patients. Tick marks indicate censoring of data. CI, confidence interval; NE, not estimable.

active TKI, to amivantamab—chemotherapy. The MARIPOSA-2 study shows that amivantamab—chemotherapy by itself can prevent or delay CNS recurrence. A similar improvement was seen among patients with a history of brain metastasis who had not received prior brain radiation, strengthening this conclusion. The mechanism by which amivantamab improves intracranial PFS could either be through direct antitumor effects or indirectly through immune-based mechanisms.

Despite limited prospective data, third-generation TKIs are frequently continued after progression in combination with chemotherapy in an effort to mitigate development of

Table 3. Treatment-emergent adverse events

Event, *n* (%)	Chemotherapy (*n* = 243)		Amivantamab—chemotherapy (*n* = 130)		Amivantamab—lazertinib—chemotherapy (*n* = 263)	
Any event	227 (93)		130 (100)		263 (100)	
Grade ≥3	117 (48)		94 (72)		242 (92)	
Any serious event	49 (20)		42 (32)		137 (52)	
Any event resulting in death	3 (1)		3 (2)		14 (5)	
Any event leading to:						
Interruptions of any study agent	81 (33)		84 (65)		202 (77)	
Reductions of any study agent	37 (15)		53 (41)		171 (65)	
Discontinuations of any study agent	9 (4)		24 (18)		90 (34)	
Adverse events[a]	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Neutropenia[b]	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
Thrombocytopenia[b]	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)
Anemia	97 (40)	23 (9)	51 (39)	15 (12)	141 (54)	48 (18)
Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
Nausea	90 (37)	2 (1)	58 (45)	1 (1)	131 (50)	16 (6)
Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
Stomatitis	21 (9)	0	41 (32)	1 (1)	120 (46)	24 (9)
Leukopenia	68 (28)	23 (9)	37 (28)	26 (20)	106 (40)	71 (27)
Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
Constipation	72 (30)	0	50 (38)	1 (1)	96 (37)	3 (1)
Decreased appetite	51 (21)	3 (1)	40 (31)	0	85 (32)	7 (3)
Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Vomiting	42 (17)	1 (0.4)	32 (25)	1 (1)	76 (29)	10 (4)
Fatigue	47 (19)	4 (2)	36 (28)	4 (3)	69 (26)	15 (6)
Diarrhea	16 (7)	1 (0.4)	18 (14)	1 (1)	68 (26)	10 (4)
Asthenia	40 (16)	5 (2)	34 (26)	1 (1)	67 (25)	14 (5)
Dermatitis acneiform	7 (3)	0	26 (20)	5 (4)	62 (24)	17 (6)
Alanine aminotransferase increased	67 (28)	10 (4)	26 (20)	7 (5)	55 (21)	14 (5)
Hypokalemia	15 (6)	6 (2)	24 (18)	6 (5)	55 (21)	16 (6)
COVID-19	25 (10)	0	27 (21)	2 (2)	44 (17)	0
Hypocalcemia	9 (4)	0	16 (12)	1 (1)	44 (17)	3 (1)
Aspartate aminotransferase increased	57 (23)	0	19 (15)	1 (1)	43 (16)	7 (3)
Hyponatremia	16 (7)	2 (1)	13 (10)	5 (4)	42 (16)	10 (4)
Pruritus	17 (7)	0	20 (15)	0	30 (11)	0
Adverse events of special interest	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Rash[c]	30 (12)	0	92 (71)	13 (10)	197 (75)	40 (15)
Venous thromboembolism[d]	11 (5)	7 (3)	13 (10)	3 (2)	58 (22)	17 (6)
Interstitial lung disease[e]	0	0	2 (2)	1 (1)	7 (3)	5 (2)

The safety population included all randomized patients who received at least one dose of any study treatment.
COVID-19, coronavirus disease 2019.
[a]Listed are adverse events by preferred term of all grades reported in ≥15% of patients in any treatment arm.
[b]For the amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy arms, ≥80% occurred in cycle 1 (within 21 days of treatment).
[c]Included the following preferred terms: rash, dermatitis acneiform, rash maculopapular, erythema, acne, rash pruritic, rash erythematous, rash macular, drug eruption, folliculitis, dermatitis, skin lesion, rash pustular, papule, rash follicular, exfoliative rash, pustule, rash papular, and skin exfoliation.
[d]Included the following preferred terms: pulmonary embolism, deep vein thrombosis, embolism, renal vein thrombosis, venous thrombosis limb, embolism venous, jugular vein thrombosis, superficial vein thrombosis, thrombophlebitis, and thrombosis.
[e]Included the following preferred terms: pneumonitis and interstitial lung disease.

CNS metastases.[37] Data from this study and others indicate an elevated risk of cytopenic events when third-generation TKIs are administered concurrently with carboplatin.[34,38-40] This toxicity necessitated a regimen change in the amivantamab—lazertinib—chemotherapy arm of this study. The rates of hematologic AEs were lower for amivantamab—chemotherapy versus amivantamab—lazertinib—chemotherapy. Notably, neutropenia was a leading cause of grade 3 or higher AEs for both amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy. Blood draws were carried out weekly in cycle 1, which captured transient decreases in neutrophil and platelet counts at the expected chemotherapy-induced nadir. Neutrophil and platelet counts were recovered by cycle 2 day 1 and stabilized. The rates of treatment discontinuations due to neutropenia and incidence of febrile neutropenia were low, further suggesting that the majority of neutropenia events were not clinically impactful. Consistent with prior reports, amivantamab-containing arms also had a higher incidence of EGFR- and MET-related AEs.[33,41] The majority of these events were not serious (<2%) and of grade 1 or 2. In particular, discontinuations due to rash were infrequent, indicating rash was manageable through dose modifications and standard mitigation approaches. The incidences of infusion-related reactions in the amivantamab-containing arms were lower than reported for amivantamab monotherapy (56%-58% versus 67%). The majority were of grade 1-2 and did not lead to dose reductions or discontinuations. VTE rates were higher in patients receiving amivantamab—lazertinib—chemotherapy relative to the other arms, which

is consistent with prior reports.[35] There were no fatal VTEs, the events occurred early, and the majority were grade 1 or 2. It should be noted that despite the recommendation to use prophylactic anticoagulation for the first 4 months of treatment, utilization of anticoagulation was limited in MARIPOSA-2. The fact that the vast majority (>98%) of patients experiencing a venous thromboembolic event were not on anticoagulation, as well as the established safety and efficacy of anticoagulation in this population,[42,43] implies that compliance with prophylactic anticoagulation is likely to mitigate this risk.

Amivantamab—chemotherapy has a manageable toxicity profile, as noted by the low rates of discontinuations of all study agents due to treatment-related AEs. It should be noted that it is likely that the safety profile of amivantamab—lazertinib—chemotherapy will improve by not giving all four drugs simultaneously. Given the change to the amivantamab—lazertinib—chemotherapy regimen during the trial, more follow-up is required to rigorously characterize the safety and efficacy of the modified regimen.

At present, there are no targeted therapies approved in the post-osimertinib setting. Two studies of immunotherapy—chemotherapy regimens have recently failed to show benefit over chemotherapy in the TKI-resistant setting.[17,18] This highlights the unmet need in this patient population. Additionally, the ideal treatment in the second-line setting may further evolve as there are several novel regimens being evaluated in the first-line setting. At this time, however, amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy are the first regimens to demonstrate efficacy over chemotherapy in the post-osimertinib setting and could represent a new standard of care.

MARIPOSA-2 did not require pretreatment tissue biopsies and instead collected blood samples for evaluating circulating tumor DNA (ctDNA). An NGS analysis of baseline ctDNA is planned; however, identification of ctDNA-based biomarkers has not previously been predictive of response.[26,31] In addition, amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy improved clinical outcomes without the need for biomarker preselection.

In summary, PFS and key secondary endpoints, such as objective response rate, duration of response, and intracranial PFS, were significantly improved with amivantamab—chemotherapy and amivantamab—lazertinib—chemotherapy compared with chemotherapy in patients with *EGFR*-mutated advanced NSCLC with disease progression on or after osimertinib.

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DATA SHARING

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

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