Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study

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ABSTRACT

PURPOSE Phase III studies of intravenous amivantamab demonstrated efficacy across epidermal growth factor receptor (*EGFR*)–mutated advanced non–small cell lung cancer (NSCLC). A subcutaneous formulation could improve tolerability and reduce administration time while maintaining efficacy.

PATIENTS AND METHODS Patients with *EGFR*-mutated advanced NSCLC who progressed after osimertinib and platinum-based chemotherapy were randomly assigned 1:1 to receive subcutaneous or intravenous amivantamab, both combined with lazertinib. Coprimary pharmacokinetic noninferiority end points were trough concentrations (C_{trough}; on cycle-2-day-1 or cycle-4-day-1) and cycle-2 area under the curve (AUC_{D1-D15}). Key secondary end points were objective response rate (ORR) and progression-free survival (PFS). Overall survival (OS) was a predefined exploratory end point.

RESULTS Overall, 418 patients underwent random assignment (subcutaneous group, n = 206; intravenous group, n = 212). Geometric mean ratios of C_{trough} for subcutaneous to intravenous amivantamab were 1.15 (90% CI, 1.04 to 1.26) at cycle-2-day-1 and 1.42 (90% CI, 1.27 to 1.61) at cycle-4-day-1; the cycle-2 AUC_{D1-D15} was 1.03 (90% CI, 0.98 to 1.09). ORR was 30% in the subcutaneous and 33% in the intravenous group; median PFS was 6.1 and 4.3 months, respectively. OS was significantly longer in the subcutaneous versus intravenous group (hazard ratio for death, 0.62; 95% CI, 0.42 to 0.92; nominal $P = .02$). Fewer patients in the subcutaneous group experienced infusion-related reactions (IRRs; 13% *v* 66%) and venous thromboembolism (9% *v* 14%) versus the intravenous group. Median administration time for the first infusion was reduced to 4.8 minutes (range, 0-18) for subcutaneous amivantamab and to 5 hours (range, 0.2-9.9) for intravenous amivantamab. During cycle-1-day-1, 85% and 52% of patients in the subcutaneous and intravenous groups, respectively, considered treatment convenient; the end-of-treatment rates were 85% and 35%, respectively.

CONCLUSION Subcutaneous amivantamab-lazertinib demonstrated noninferiority to intravenous amivantamab-lazertinib, offering a consistent safety profile with reduced IRRs, increased convenience, and prolonged survival.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Data Supplement
- Protocol

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CONTEXT

Key Objective

Is subcutaneous amivantamab combined with lazertinib noninferior (for pharmacokinetics and efficacy) versus intravenous amivantamab-lazertinib, and does it have a similar safety profile?

Knowledge Generated

Subcutaneous amivantamab-lazertinib demonstrated noninferior pharmacokinetics and objective response rates, with potentially longer response duration, progression-free survival, and overall survival compared with intravenous amivantamab-lazertinib. The subcutaneous formulation also exhibited reduced infusion-related reactions and venous thromboembolic events, with shorter treatment administration times and enhanced patient convenience compared with the intravenous formulation.

Relevance *(T.E. Stinchcombe)*

The subcutaneous formulation of amivantamab in combination with lazertinib or with carboplatin and pemetrexed may become a treatment option in the future.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

INTRODUCTION

Amivantamab is an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell–directing activity.[1-5] The intravenous formulation of amivantamab is approved in combination with chemotherapy in the first-line setting (phase III PAPILLON trial) and as a monotherapy after disease progression on platinum-based chemotherapy (phase I CHRYSALIS trial) in patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with *EGFR* exon 20 insertion mutations.[6]

Amivantamab has been combined with lazertinib, a central nervous system–penetrant, third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI). Amivantamab-lazertinib demonstrated superior progression-free survival (PFS) versus osimertinib in patients with treatment-naïve, *EGFR*-mutated advanced NSCLC on the basis of the phase III MARIPOSA trial.[7]

Infusion-related reactions (IRRs) are observed in two thirds of patients receiving intravenous amivantamab, with most occurring on cycle-1-day-1 and being grade 1 to 2.[8] The initial dose of intravenous amivantamab is split over 2 days to reduce IRRs, resulting in a minimum total infusion time of 2-4 hours.[6] The subcutaneous formulation of amivantamab was first evaluated in the phase I PALOMA trial, revealing low rates of IRRs and associated symptoms, with an administration time ≤7 minutes for the once-every-2-week and once-every-3-week regimens, and up to 10 minutes for the once-every-4-week regimen.[9,10]

The goal of the subcutaneous amivantamab development program is to reduce administration time and improve patient convenience. PALOMA-3 (ClinicalTrials.gov identifier: NCT05388669) is a phase III, international, randomized trial assessing the noninferiority of pharmacokinetics, efficacy, and safety of subcutaneous versus intravenous amivantamab, both combined with lazertinib, in patients with *EGFR*-mutated, advanced NSCLC after disease progression on osimertinib and platinum-based chemotherapy.

PATIENTS AND METHODS

Patients

Eligible patients were age 18 years and older, had confirmed advanced or metastatic NSCLC harboring classical *EGFR* exon 19 deletions (Ex19del) or exon 21 L858R mutations with disease progression on or after osimertinib (or another approved third-generation EGFR-TKI) and platinum-based chemotherapy, irrespective of sequence. For additional criteria, see the protocol (online only).

Study Design and Treatment

Patients were randomly assigned (1:1) to receive subcutaneous amivantamab-lazertinib or intravenous amivantamab-lazertinib in 28-day cycles (Appendix Fig A1, online only). Subcutaneous amivantamab (concentration, 160 mg/mL), coformulated with hyaluronidase (rHuPH20), was administered by manual injection at a dose of 1,600 mg (2,240 mg for ≥80 kg weight) once-weekly for the first 4 weeks and every 2 weeks thereafter.[9] Intravenous amivantamab (concentration, 50 mg/mL) was administered at the approved dose of 1,050 mg (1,400 mg for ≥80 kg weight) on the same interval, with the first infusion split over 2 days (350 mg on cycle-1-day-1, the remainder on cycle-1-day-2). Lazertinib was administered orally at a dose of 240 mg once daily.

Random assignment was stratified by history of brain metastases (yes or no), *EGFR* mutation type (Ex19del *v* L858R), race (Asian *v* non-Asian), and type of last therapy (osimertinib *v* chemotherapy).

An increased risk of venous thromboembolism (VTE) associated with intravenous amivantamab-lazertinib was initially observed in the MARIPOSA trial.[7] This increase appears specific to amivantamab-lazertinib, as amivantamab monotherapy, lazertinib monotherapy, and amivantamab-chemotherapy did not show notable rises in VTE incidence.[11-14] Consequently, the study protocol was amended to recommend prophylactic anticoagulation for the first 4 months of amivantamab-lazertinib treatment as per local guidelines.

End Points and Assessments

The coprimary pharmacokinetic outcomes for noninferiority were trough concentrations (C_{trough}; either predose on cycle-2-day-1 or at steady state [cycle-4-day-1], per regional health authority guidance) and area under the curve from cycle-2-day-1 to day-15 (AUC_{D1-D15}). Key secondary outcomes were objective response rate (ORR) and PFS. Overall survival (OS) was a predefined exploratory end point. A complete list of outcomes and definitions is available in the protocol.

Disease assessments (computed tomography, magnetic resonance imaging, or other imaging) were performed within 28 days before random assignment, then at 6 weeks (maximum, 7 weeks) after random assignment and subsequently every 6 weeks (within a 1-week window) for the first 18 months and every 12 weeks (within a 1-week window) thereafter until disease progression. All response assessments were performed by the investigator according to RECIST, v1.1. All patients underwent brain imaging at baseline; subsequent imaging was performed every 6 weeks in patients with baseline brain metastases or as clinically indicated.

Adverse events (AEs), vital signs, and laboratory tests were assessed at each visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0. Pharmacokinetic and immunogenicity assessments for amivantamab were conducted using validated assays on blood serum and plasma samples collected throughout the trial until the end of treatment. Patient-reported cancer therapy satisfaction was assessed using a modified version of the Therapy Administration Satisfaction Questionnaire (TASQ), completed by patients after treatment administration in cycle-1, cycle-3, and at the end of treatment.

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 Council for Harmonisation), and applicable regulatory and country-/territory-specific requirements. The protocol was approved by the local institutional review board and independent ethics committees of the participating centers. Patients provided written informed consent at screening. Protocol amendments made after the study started are described in the protocol.

Statistical Analysis

The pharmacokinetic analysis included patients who received all doses without modification and provided the required pharmacokinetic samples through the final required sample relevant to the end point. Efficacy analysis included all randomly assigned patients. Safety analysis included all patients who received ≥1 dose of any treatment. For calculating primary and key secondary outcomes, we estimated that a sample size of 400 patients would provide >95% power for a one-sided alpha of .05 allocated to each of the coprimary pharmacokinetic end points and 80% power with a one-sided alpha of .025 allocated to ORR. For the coprimary end points, the power analysis assumes true geometric mean ratios of C_{trough} and AUC_{D1-D15} to be 1 between the two treatment groups, and a coefficient of variation (CV) of 56% for both end points. Additional details can be found in Section 9 of the protocol.

The primary hypotheses were that the lower bounds of the 90% CI for the geometric mean ratios for subcutaneous versus intravenous amivantamab would be ≥80% (noninferiority margin of 20%) for both coprimary pharmacokinetic end points. The noninferiority criterion for the pharmacokinetic primary end point is based on the US Food and Drug Administration–recommended lower limit for the bioequivalence.[15,16] ORR was analyzed using logistic regression, with noninferiority established if the lower bound of the relative risk's 95% CI was ≥60% (on the basis of regulatory precedence from other subcutaneous formulations[17]; additional details can be found on the statistical analysis plan, Data Supplement, online only). PFS was evaluated using the *P* value generated from the stratified log-rank test, with *EGFR* mutation type, Asian race, history of brain metastasis, and last therapy as stratification factors. The hazard ratio (HR) and 95% CI were estimated using a stratified Cox regression model, with treatment as the sole explanatory variable. Medians and corresponding 95% CIs were estimated using the Kaplan-Meier method. A hierarchical testing approach was used for the coprimary pharmacokinetic end points (noninferiority, at a two-sided alpha of .05), followed by the key secondary end points of ORR (noninferiority) and then PFS (superiority). The key secondary end points were tested using a combined two-sided alpha of .05.

Analyses of additional secondary or other outcomes, including subgroup analyses, were not part of hypothesis testing in the trial, and these results are reported as descriptive statistics without adjustment for multiplicity. All

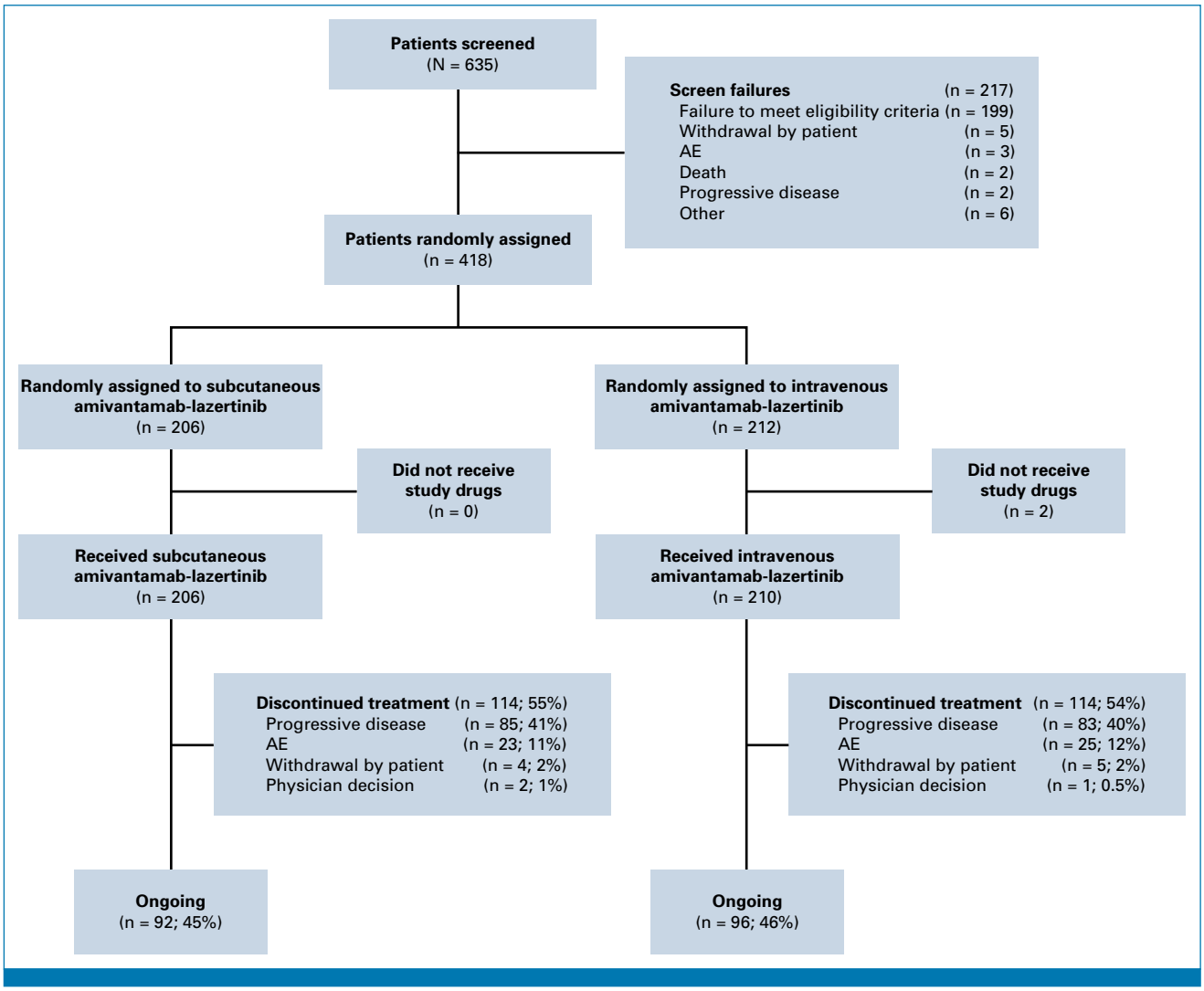

FIG 1. CONSORT diagram of patient disposition. AE, adverse event.

data reported here are based on the primary analysis and were reported before the January 3, 2024, data cutoff date.

RESULTS

Patients

From August 2022 to October 2023, 635 patients were screened and 418 were randomly assigned (206 to subcutaneous amivantamab-lazertinib and 212 to intravenous amivantamab-lazertinib; Fig 1). Overall, 416 patients received ≥1 dose of trial treatment. Pharmacokinetic samples were available from 414 patients. Demographic and baseline characteristics were well balanced (Table 1); median number of previous therapy lines was 2 (range, 1-5 [subcutaneous], 1-4 [intravenous]). Most patients were female, were Asian or White, and had never smoked.

At a median follow-up of 7.0 months (range, 0.1-14.4), median treatment duration was 4.7 months (range, 0.1-13.2) in the subcutaneous group and 4.1 (range, 0.0-13.2) in the intravenous group. Median duration of amivantamab administration on cycle-1-day-1 was 4.8 minutes (range, 0-18) in the subcutaneous and 5.0 hours (range, 0.2-9.9) for the first infusion on cycle-1-day-1 in the intravenous group; corresponding values on cycle-3-day-1 were 4.8 minutes (range, 0-12) and 2.3 hours (range, 0.5-4.4). At data cutoff, 92 (45%) and 96 (46%) patients were undergoing treatment in the subcutaneous and intravenous groups, respectively. Time to amivantamab discontinuation is shown in Appendix Figure A2.

Pharmacokinetics

Mean (%CV) C_{trough} at cycle-2-day-1 was 365 (33) μg/mL and 314 (32) μg/mL in the subcutaneous and intravenous groups, respectively; corresponding values at cycle-4-day-1 were 224 (39) μg/mL and 162 (42) μg/mL (Table 2). The geometric mean ratio for C_{trough} for subcutaneous to intravenous group was 1.15 (90% CI, 1.04 to 1.26) at cycle-2-

TABLE 1. Demographic and Clinical Characteristics of Patients at Baseline

Characteristic	Subcutaneous Group (n = 206)	Intravenous Group (n = 212)
Age, years		
Median (range)	61 (35-82)	62 (29-81)
Distribution, No. (%)		
<65 years	133 (65)	120 (57)
≥65 to <75 years	55 (27)	70 (33)
≥75 years	18 (9)	22 (10)
Sex, No. (%)		
Female	138 (67)	141 (67)
Male	68 (33)	71 (33)
Race or ethnic group, No. (%)		
Asian	126 (61)	129 (61)
White	78 (38)	77 (36)
Black or African American	1 (0.5)	3 (1)
Multiple	0	1 (0.5)
Not reported	1 (0.5)	2 (0.9)
Body weight		
Median, kg (range)	61.8 (35-130)	60.1 (33-150)
Distribution, No. (%)		
<80 kg	184 (89)	184 (87)
≥80 kg	22 (11)	28 (13)
Region of enrollment, No. (%)[a]		
North America	19 (9)	30 (14)
South America	11 (5)	17 (8)
Europe	38 (18)	40 (19)
Asia	126 (61)	120 (57)
Oceania	12 (6)	5 (2)
ECOG PS, No. (%)		
0	58 (28)	61 (29)
1	148 (72)	151 (71)
History of smoking, No. (%)		
No	141 (68)	145 (68)
Yes	65 (32)	67 (32)
Median time from initial diagnosis, months (range)	34.5 (2.8-191.3)	33.7 (6.1-156.9)
Median time from metastatic diagnosis, months (range)	32.7 (0.9-169.0)	29.7 (0.6-142.6)
Histologic type, No. (%)		
Adenocarcinoma	204 (99)	207 (98)
Large cell carcinoma	1 (0.5)	1 (0.5)
Squamous cell carcinoma	1 (0.5)	3 (1)
Other	0	1 (0.5)
EGFR mutation type at random assignment, No. (%)		
Exon 19 deletion	135 (66)	138 (65)
L858R	71 (34)	74 (35)
History of brain metastasis, No. (%)		
Yes	70 (34)	72 (34)
No	136 (66)	140 (66)
Last therapy before random assignment, No. (%)		
Osimertinib	91 (44)	96 (45)
Chemotherapy	115 (56)	116 (55)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

[a]Russia was counted as part of Europe; Turkey and Israel were counted as part of Asia.

TABLE 2. Coprimary Pharmacokinetic and Key Efficacy End Points

End Point	Subcutaneous Group (n = 206)	Intravenous Group (n = 212)	Treatment Effect (95% CI)	*P*
Coprimary pharmacokinetic end points[a]				
C_{trough}, μg/mL (%CV)			Geometric mean ratio (90% CI)	
Cycle-2-day-1	365 (33)	314 (32)	1.15 (1.04 to 1.26)	
Cycle-4-day-1 (steady state)	224 (39)	162 (42)	1.43 (1.27 to 1.61)	
AUC_{D1-D15}, μg·h/mL (%CV)			Geometric mean ratio (90% CI)	
Cycle 2	142,236 (31)	135,552 (24)	1.03 (0.98 to 1.09)	
Secondary end points				
Objective response[b]				
Patients, % (95% CI)	30 (24 to 37)	33 (26 to 39)	Relative risk for noninferiority, 0.92 (0.70 to 1.23)[c]	.001
Progression-free survival				
Median, mo (95% CI)	6.1 (4.3 to 8.1)	4.3 (4.1 to 5.7)	HR, 0.84 (0.64 to 1.10)	.20
Patients, % (95% CI)				
At 6 months	50 (43 to 58)	42 (35 to 50)		
At 12 months	37 (28 to 46)	20 (8 to 35)		
Overall survival				
Median, mo (95% CI)	12.9 (12.9 to NE)	NE (10.2 to NE)	HR, 0.62 (0.42 to 0.92)[d]	.02[d]
Patients, % (95% CI)				
At 6 months	85 (79 to 89)	75 (68 to 80)		
At 12 months	65 (52 to 74)	51 (37 to 64)		

Abbreviations: %CV, % coefficient of variation; AUC_{D1-D15}, area under the curve from cycle-2 day-1 to day-15; C_{trough}, observed serum concentration of amivantamab at steady state; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; NE, not estimable; TKI, tyrosine kinase inhibitor.

[a]The pharmacokinetic population for evaluating the coprimary pharmacokinetic end points included all patients who received all doses without dose modifications before the respective end point and who provided the pharmacokinetic samples necessary to derive each parameter. The efficacy population included all the patients who had undergone random assignment.

[b]The objective response (complete or partial response as best response) was assessed by the investigator among all responders.

[c]Odds ratio (95% CI), 0.87 (0.58 to 1.32); $P = .52$. *P* value is calculated via a logistic regression model stratified by brain metastases at baseline (yes *v* no), *EGFR* mutation (L858R *v* Ex19del), race (Asian *v* non-Asian), and last therapy (osimertinib [or another third-generation EGFR-TKI] *v* chemotherapy).

[d]For overall survival, 95% CIs were not adjusted for multiplicity and should not be used in place of hypothesis testing; *P* value is nominal.

day-1 and 1.43 (90% CI, 1.27 to 1.61) at cycle-4-day-1. Cycle-2 AUC_{D1-D15} mean (%CV) was 142,236 (31) μg·h/mL and 135,552 (24) μg·h/mL in the subcutaneous and intravenous groups, respectively. The geometric mean ratio for cycle-2 AUC_{D1-D15} was 1.03 (90% CI, 0.98 to 1.09). These results indicate that the noninferiority criteria were met. Observed amivantamab concentration-time profiles and boxplots of C_{trough} and AUC_{D1-D15} are shown in Appendix Figure A3.

Treatment-emergent antiamivantamab antibodies were detected in one (0.6%) patient in the subcutaneous and none in the intravenous group. Treatment-emergent anti-rHuPH20 antibodies occurred in 15 (8%) patients in the subcutaneous group without impact on amivantamab pharmacokinetics.

Efficacy

An objective response (complete or partial) was reported in 30% of patients (95% CI, 24 to 37) in the subcutaneous group and 33% (95% CI, 26 to 39) in the intravenous group (relative risk, 0.92; 95% CI, 0.70 to 1.23; Table 2 and Appendix Fig A4). The ORR in the subcutaneous group met the noninferiority criterion (lower 95% CI bound equals 70%) by retaining ≥60% of the ORR in the intravenous group. Objective response for predefined subgroups is shown in Figure 2A. Median time to response was 1.5 months (range, 1.2-6.9) in the subcutaneous group and 1.5 months (range, 1.2-9.9) in the intravenous group. Among confirmed responders, median response duration (DoR) was 11.2 months (95% CI, 6.1 to not estimable [NE]) in the subcutaneous group and 8.3 months (95% CI, 5.4 to NE) in the intravenous group; 29% and 14% of patients, respectively, had a DoR ≥6 months (Appendix Fig A5 and Table A1).

The percentage of patients exhibiting stable disease was 45% in the subcutaneous group and 38% in the intravenous group. Disease control rate was 75% (95% CI, 69 to 81) in the subcutaneous group and 71% (95% CI, 64 to 77) in the intravenous group (Appendix Table A1). PFS was tested for

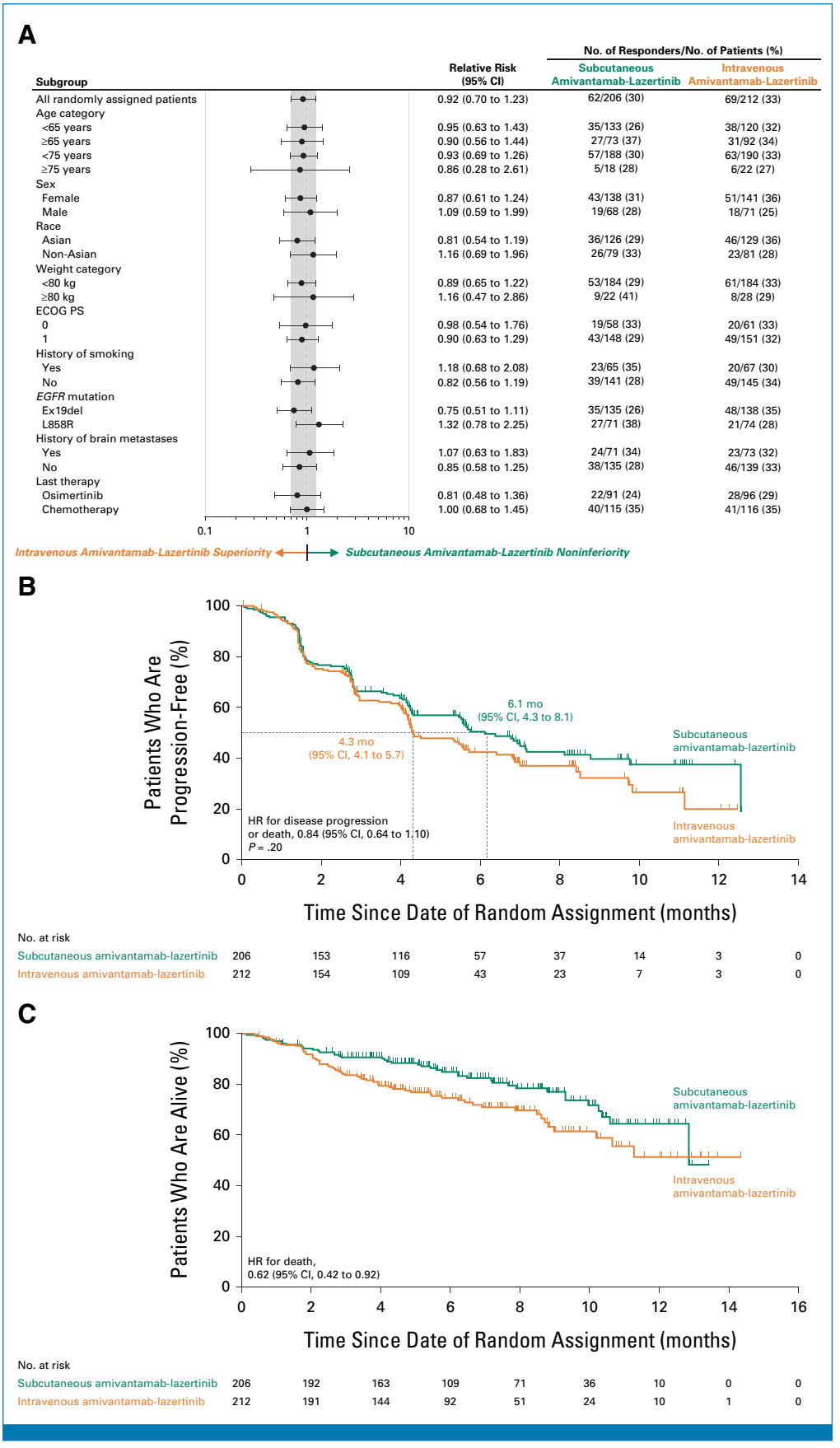

FIG 2. (A) Objective response forest plot, (B) PFS, and (C) OS. The efficacy population included all patients who had undergone random assignment. (A) The shaded area indicates 95% CIs for the (continued on following page)

FIG 2. (Continued). relative risk in all patients; the subgroup analyses were not part of the hypothesis testing and results are reported without adjustment for multiplicity. (B, C) The dashed lines indicate the median PFS and OS, respectively, in the two groups, and the tick marks indicate censoring of data. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

superiority of subcutaneous versus intravenous amivantamab, with a median PFS of 6.1 months (95% CI, 4.3 to 8.1) and 4.3 months (95% CI, 4.1 to 5.7), respectively, but did not reach statistical significance (HR for disease progression or death, 0.84; 95% CI, 0.64 to 1.10; $P = .20$; Fig 2B).

Death occurred in 43 patients in the subcutaneous and 62 patients in the intravenous group, with 35/43 (81%) and 50/62 (81%) deaths caused by progressive disease, respectively. The percentage of patients who were alive at 6 and 12 months, respectively, was 85% (95% CI, 79 to 89) and 65% (95% CI, 52 to 74) in the subcutaneous group, and 75% (95% CI, 68 to 80) and 51% (95% CI, 37 to 64) in the intravenous group. OS was significantly longer for the subcutaneous compared with the intravenous group (HR for death, 0.62; 95% CI, 0.42 to 0.92; nominal $P = .02$; Fig 2C).

Safety

Most patients had ≥1 AE (Table 3). The most common grade ≥3 AEs (≥5% in either group) were dermatitis acneiform (9% and 6% in the subcutaneous and intravenous groups, respectively) and lymphopenia (<1% and 8%). Serious AEs were reported in 29% and 30% of patients in the subcutaneous and intravenous groups, respectively (Appendix Table A2).

The proportion of patients reporting an IRR was 13% in the subcutaneous group and 66% in intravenous group (Fig 3), with one (0.5%) and eight (4%) patients experiencing a grade 3 event, respectively (no grade 4 or 5 events were reported). All infusion-related AEs ranged between 0% and 6% in the subcutaneous group and 2% and 20% in the intravenous group. Most IRRs occurred during cycle-1 (Appendix Fig A6). There were no discontinuations because of IRRs in the subcutaneous group versus four (2%) in the intravenous group.

VTE was reported in 9% of patients in the subcutaneous group and 14% in the intravenous group, with pulmonary embolism and deep-vein thrombosis being the most common (Appendix Table A3). Among all VTE, most occurred in the first 4 months (74% and 67% in the subcutaneous and intravenous groups, respectively). Overall, 80% and 81% of patients in the subcutaneous and intravenous groups, respectively, received prophylactic anticoagulation (Appendix Table A4). Among those receiving prophylactic anticoagulation, VTE occurred in 7% and 12% of patients, respectively; the rates of VTE among patients who did not receive anticoagulation were 17% and 26%, respectively (Appendix Tables A5 and A6). Grade ≥3 bleeding events occurred in 2% and 0.6% of patients receiving anticoagulation in the subcutaneous and intravenous groups, respectively; one patient in the subcutaneous group receiving anticoagulation discontinued treatment because of bleeding.

AEs leading to dose interruptions, reductions, and discontinuations of any trial agent are shown in Table 3. The dose reduction rate was 31% in the subcutaneous group and 25% in the intravenous group; corresponding rates because of grade ≥3 AEs were 3% and 4%, respectively. Rash was the leading cause for dose reductions in the subcutaneous and intravenous groups (8% *v* 4%) with similar incidence of all-grade rash (46% *v* 43%) and grade ≥3 rash (3% *v* 4%) between both groups (Appendix Table A7). The median duration of rash was 31 days in the subcutaneous group and 44 days in the intravenous group. Most common reasons for discontinuation are presented in Appendix Table A7. Discontinuation of all agents because of treatment-related AEs was 9% and 12% in the subcutaneous and intravenous groups, respectively. Treatment-related AEs are shown in Appendix Table A8.

Death due to AEs occurred in seven (3%) and 10 (5%) patients in the subcutaneous and intravenous groups, respectively. All grade 5 AEs are listed in Appendix Table A9.

Patient Convenience

The subcutaneous injection during cycle-1-day-1 was reported as very convenient or convenient by 85% of patients, versus 52% of patients for the intravenous infusion (nominal $P < .001$; Fig 4). Data at cycle-3-day-1 were consistent with cycle-1-day-1. At the end of treatment, the subcutaneous injection was reported as very convenient or convenient by 85% of patients versus 35% for the intravenous infusion (nominal $P < .001$).

DISCUSSION

Subcutaneous amivantamab-lazertinib demonstrated noninferior pharmacokinetics and antitumor activity (objective response) compared with intravenous amivantamab-lazertinib. The geometric mean ratio for C_{trough} was 1.15 at cycle-2-day-1 and 1.43 at cycle-4-day-1, indicating that noninferior trough concentrations were maintained with subcutaneous versus intravenous administration, although total systemic exposure (cycle-2 AUC_{D1-D15}) remained similar between groups. Consistent with the established flat exposure-safety relationships previously reported,[18] the higher C_{trough} observed with subcutaneous amivantamab-

TABLE 3. Overview of AEs

AE[a]	Subcutaneous Group (n = 206), No. (%)		Intravenous Group (n = 210), No. (%)	
Any event	204 (99)		209 (99)	
Grade ≥3	107 (52)		118 (56)	
Any serious event	59 (29)		64 (30)	
Any event resulting in death	7 (3)		10 (5)	
Any event leading to:				
Interruption of any study agent[b]	127 (62)		127 (60)	
Reduction of any study agent	63 (31)		52 (25)	
Discontinuation of any study agent	26 (13)		29 (14)	
AEs reported in ≥15% of patients in either group[c]	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Paronychia	111 (54)	8 (4)	108 (51)	3 (1)
Hypoalbuminemia	96 (47)	9 (4)	77 (37)	8 (4)
Rash	95 (46)	8 (4)	91 (43)	8 (4)
Dermatitis acneiform	64 (31)	18 (9)	69 (33)	12 (6)
Nausea	60 (29)	1 (0.5)	52 (25)	3 (1)
Stomatitis	57 (28)	1 (0.5)	69 (33)	5 (2)
Peripheral edema	52 (25)	6 (3)	58 (28)	1 (0.5)
Increased alanine aminotransferase	46 (22)	6 (3)	56 (27)	8 (4)
Decreased appetite	45 (22)	1 (0.5)	52 (25)	3 (1)
Fatigue	44 (21)	3 (1)	43 (20)	5 (2)
Vomiting	44 (21)	2 (1)	41 (20)	1 (0.5)
Diarrhea	43 (21)	3 (1)	39 (19)	2 (1)
Constipation	42 (20)	0	42 (20)	1 (0.5)
Headache	42 (20)	1 (0.5)	36 (17)	1 (0.5)
Increased aspartate aminotransferase	42 (20)	2 (1)	45 (21)	3 (1)
Anemia	39 (19)	4 (2)	40 (19)	5 (2)
Pruritus	33 (16)	0	25 (12)	0
Hypocalcemia	33 (16)	0	27 (13)	0
Myalgia	32 (16)	0	13 (6)	0
Asthenia	31 (15)	4 (2)	23 (11)	2 (1)
Thrombocytopenia	29 (14)	4 (2)	33 (16)	2 (1)
IRR	27 (13)	1 (0.5)	138 (66)	8 (4)

Abbreviations: AE, adverse event; IRR, infusion-related reaction.
[a]The safety population included all patients who had undergone random assignment and received at least one dose of any trial treatment.
[b]Excluding infusion-/administration-related reactions.
[c]Events in this category are listed according to decreasing incidence in the subcutaneous group.

lazertinib did not negatively affect its safety profile, as AE incidence was comparable between groups.

Although ORR was noninferior for the subcutaneous group versus the intravenous group, DoR was numerically longer and there was a higher proportion of patients with stable disease in the subcutaneous group. These results indicate that there may be a potential clinical benefit for subcutaneous amivantamab-lazertinib in disease control. Furthermore, subcutaneous amivantamab resulted in a similar time to response as intravenous amivantamab. Although statistical significance for superiority was not achieved, PFS was also numerically longer in the subcutaneous group versus the intravenous group. The predefined exploratory OS analysis showed a significantly improved survival with subcutaneous versus intravenous amivantamab-lazertinib (HR for death, 0.62, nominal $P = .02$). The observed benefit in the subcutaneous group was consistent across all efficacy end points and may be driven by better tolerability, as indicated by the longer time to treatment discontinuation. Furthermore, the impact of subcutaneous administration on lymphatic absorption and immune stimulation is unknown but may also play a role.[19-21] Although study follow-up is 7.0 months and further investigation is needed, our trial shows consistent evidence of clinically relevant improvement with subcutaneous amivantamab.

There were no unexpected toxicities from subcutaneous and intravenous amivantamab-lazertinib, consistent with previous reports.[7,22] Although dose reduction rates were

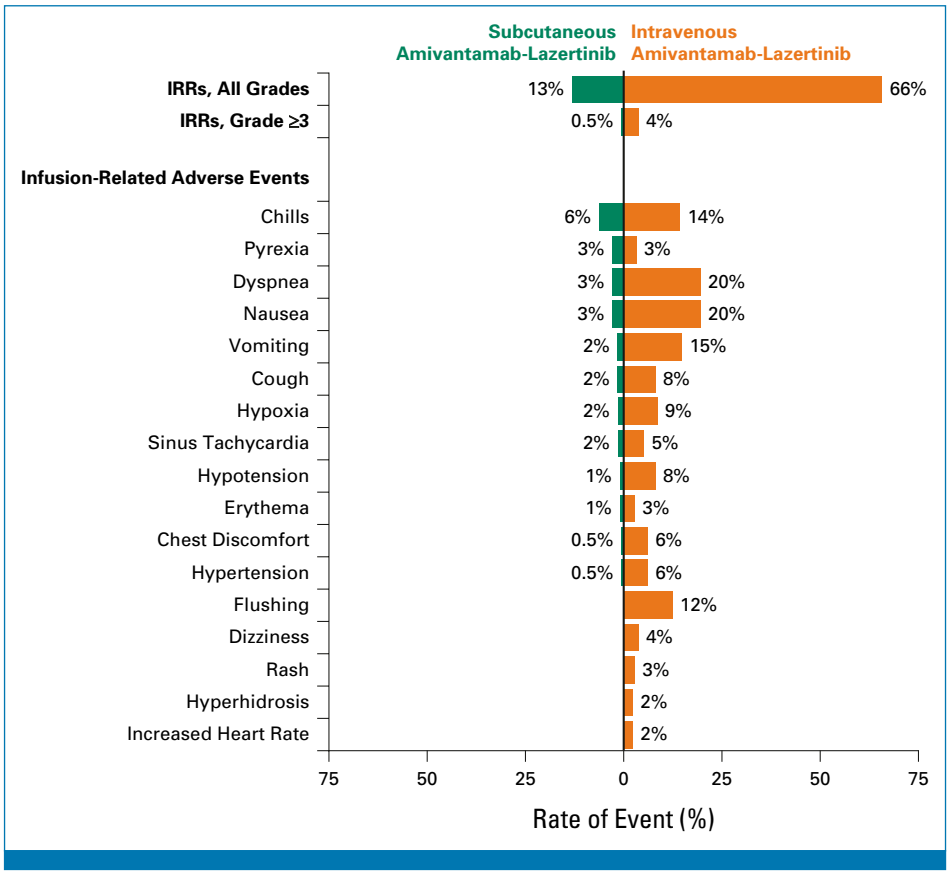

FIG 3. IRRs and infusion-related AEs. The safety population included all patients who had undergone random assignment and received at least one dose of any trial treatment. AE, adverse event; IRR, infusion-related reaction.

marginally higher in the subcutaneous group, dose reductions because of grade ≥3 AEs were comparable (3% *v* 4%). Subcutaneous amivantamab-lazertinib demonstrated a safety profile consistent with historical intravenous data, with a 5-fold reduced rate and lower severity of IRRs and a reduced administration time of <5 minutes versus up to 5 hours for intravenous amivantamab-lazertinib.[9] Patient-reported convenience was also significantly higher with subcutaneous versus intravenous administration of amivantamab.

To our knowledge, our trial is the first to prospectively evaluate the impact of prophylactic anticoagulation on the risk of VTE with amivantamab-lazertinib. The prevalence of VTE in lung cancer is 14%-30%, with higher values in patients with molecular driver alterations.[23,24] Moreover, an elevated risk of VTE in the first 4 months of treatment was specifically identified for amivantamab-lazertinib combinations in the MARIPOSA (ClinicalTrials.gov identifier: NCT04487080) and MARIPOSA-2 (ClinicalTrials.gov identifier: NCT04988295) trials.[11] For this reason, prophylactic anticoagulation was recommended, with uptake occurring in approximately 80% of all patients, leading to an observed incidence of 9% (subcutaneous) to 14% (intravenous). We also found that reduced VTE rates were observed with prophylactic anticoagulation, with low risk of clinically important bleeding across both administration routes, demonstrating that anticoagulation can be safely implemented. The safety and efficacy of prophylactic anticoagulation seen here was comparable with previous studies of patients with similar risk profiles.[25] Regardless of prophylactic anticoagulation, VTE rates were lower for the subcutaneous group than for the intravenous group.

Importantly, the increased tolerability and convenience of the subcutaneous formulation seen in PALOMA-3 may improve patient and provider experiences while maintaining efficacy. Intravenous amivantamab-based combinations are efficacious in the first- and second-line treatment of patients with advanced NSCLC harboring *EGFR* mutations.[7,12,13] The findings from our trial are expected to positively affect clinical practice and may enhance outcomes for patients with advanced NSCLC. The PALOMA-2 trial (ClinicalTrials.gov identifier: NCT05498428) is evaluating the efficacy and safety of subcutaneous amivantamab-based combinations in various patient populations across advanced NSCLC.[7,12,13] In addition, the PALOMA trial has established extended dosing intervals for subcutaneous

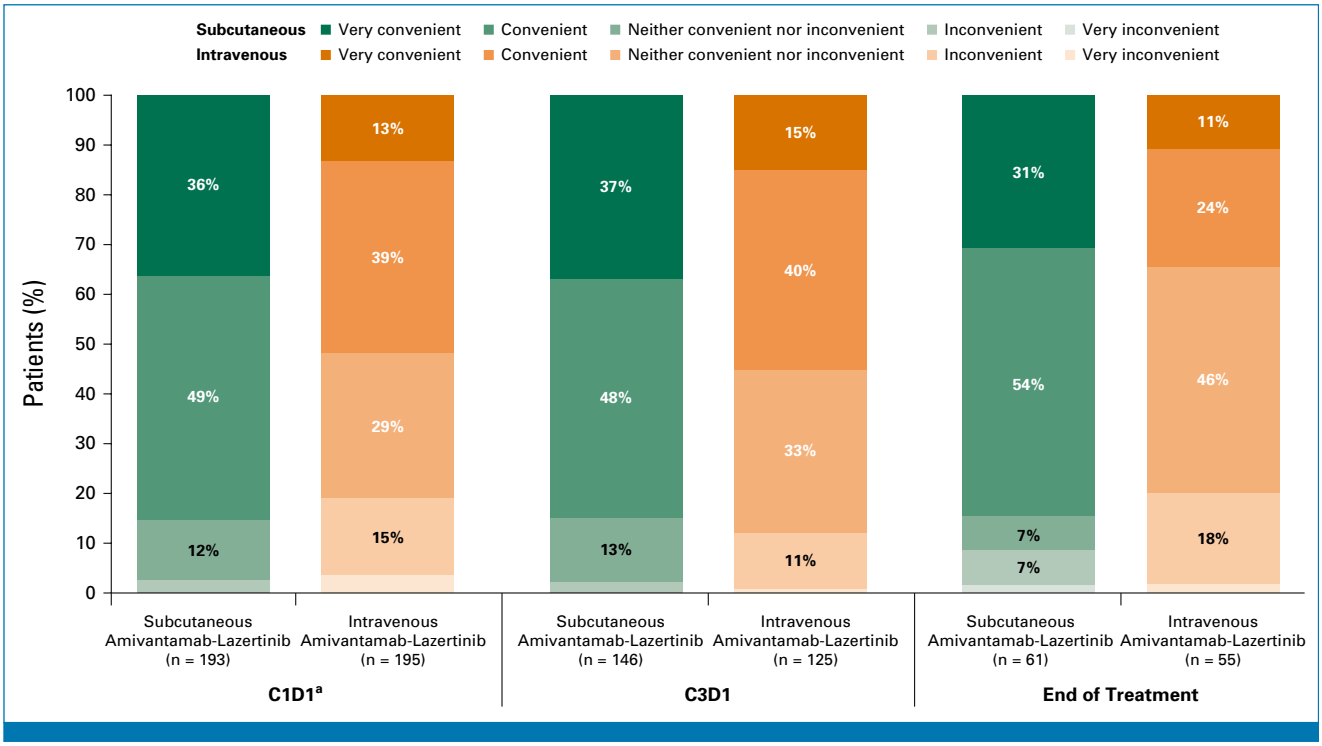

FIG 4. Patient-reported convenience of the subcutaneous injection and intravenous infusion. Item 6 of the modified TASQ asked, "How convenient is it for you to have your [IV infusion/SC injection]?" The modified TASQ was completed by patients after treatment administration in cycle-1 (baseline), cycle-3, and at EOT. EOT data could have been collected after administration of the last dose. [a]C1D2 for patients who received IV amivantamab because of split dosing. C, cycle; D, day; EOT, end of treatment; IV, intravenous; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

amivantamab administered once every 3 weeks and once every 4 weeks,[9,26] which may further increase convenience for the patient and the provider.

In summary, subcutaneous amivantamab-lazertinib demonstrated noninferior pharmacokinetics and ORR versus intravenous amivantamab-lazertinib, with numerically longer DoR and PFS. Surprisingly, significantly longer OS was observed with the subcutaneous formulation. Incidence of VTE was lower in both groups with the use of prophylactic anticoagulation. Compared with the intravenous formulation, subcutaneous amivantamab maintains efficacy, improves patient and health care provider experience, and substantially reduces the rate of IRRs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study

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No other potential conflicts of interest were reported.

APPENDIX

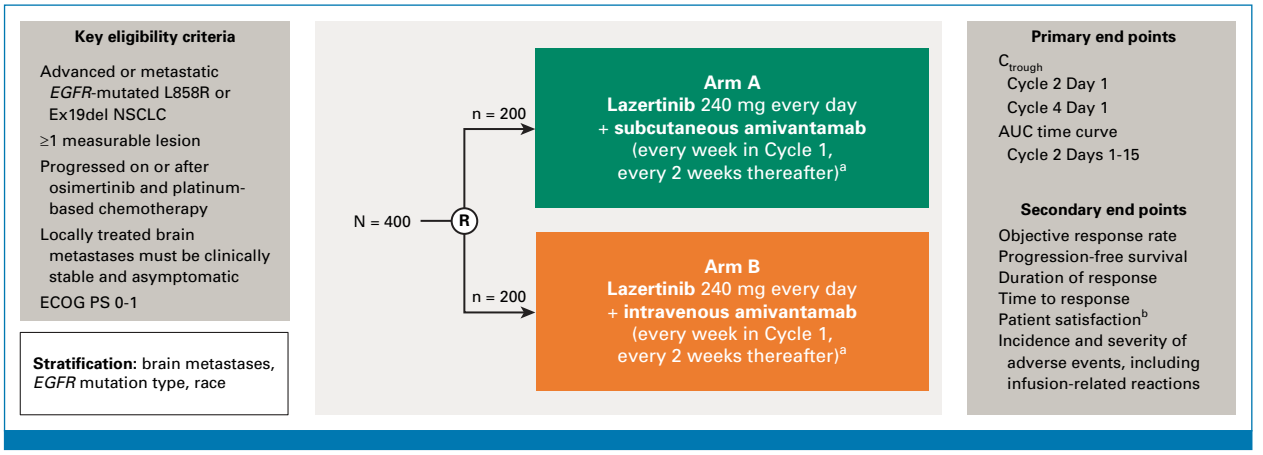

FIG A1. PALOMA-3 study design. [a]Cycle 1 for intravenous amivantamab-lazertinib: Days 1, 2 (Day 2 applies to intravenous split dose only), 8, 15, and 22; Cycle 1 for subcutaneous amivantamab-lazertinib: Days 1, 8, 15, and 22; after Cycle 1 for all: Days 1, 15 (28-day cycles). Subcutaneous amivantamab is coformulated with recombinant human hyaluronidase. [b]Assessed by using modified TASQ. AUC, area under the concentration-time curve; C_{trough}, observed serum concentration of amivantamab at steady state; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion mutation; NSCLC, non–small cell lung cancer; R, random assignment; TASQ, Therapy Administration Satisfaction Questionnaire.

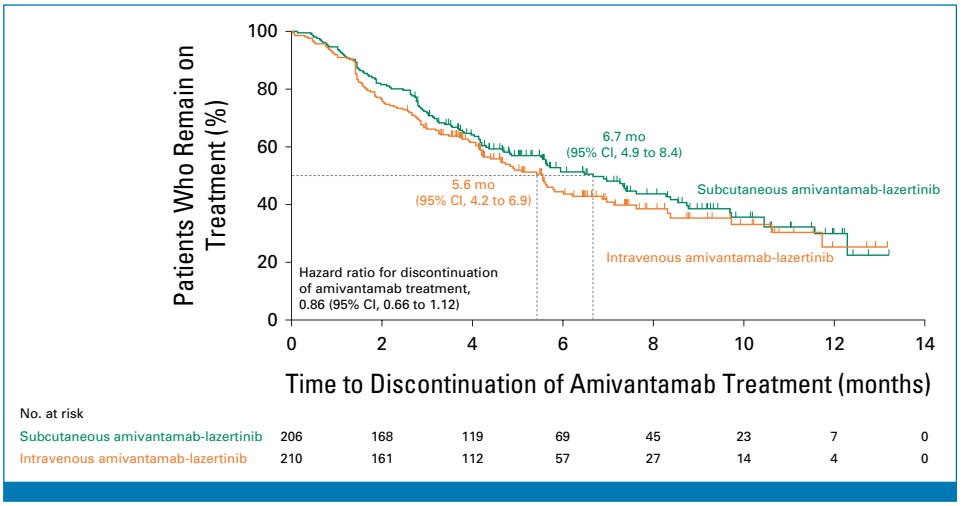

FIG A2. Time to amivantamab discontinuation. The dashed lines indicate the median time to amivantamab discontinuation in the two groups, and the tick marks indicate censoring of data.

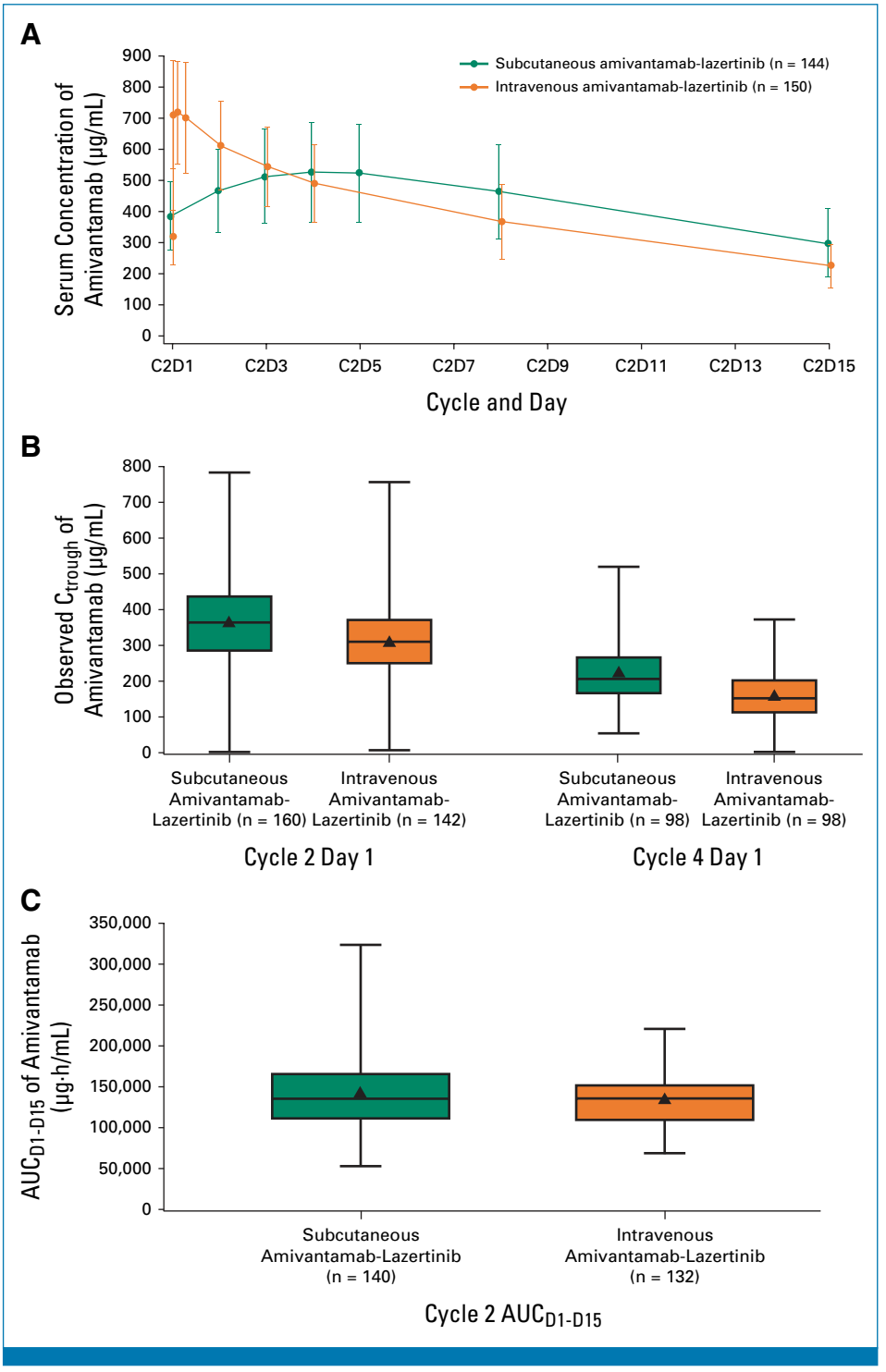

FIG A3. (A) Observed concentration-time profiles, (B) C_{trough}, and (C) AUC_{D1-D15} of amivantamab. To capture the peak concentration of intravenous amivantamab, two samples were analyzed soon after the end of infusion (at 10 minutes and 2 hours after intravenous infusion). The upper and lower end of the boxes indicate the 25th and 75th quartiles, respectively, the triangles indicate the means, the horizontal lines within the boxes indicate the medians, and the error bars indicate 95% CIs. AUC, area under the concentration-time curve; AUC_{D1-D15}, AUC between Cycle 2 Day 1 and Day 15; C, Cycle; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day.

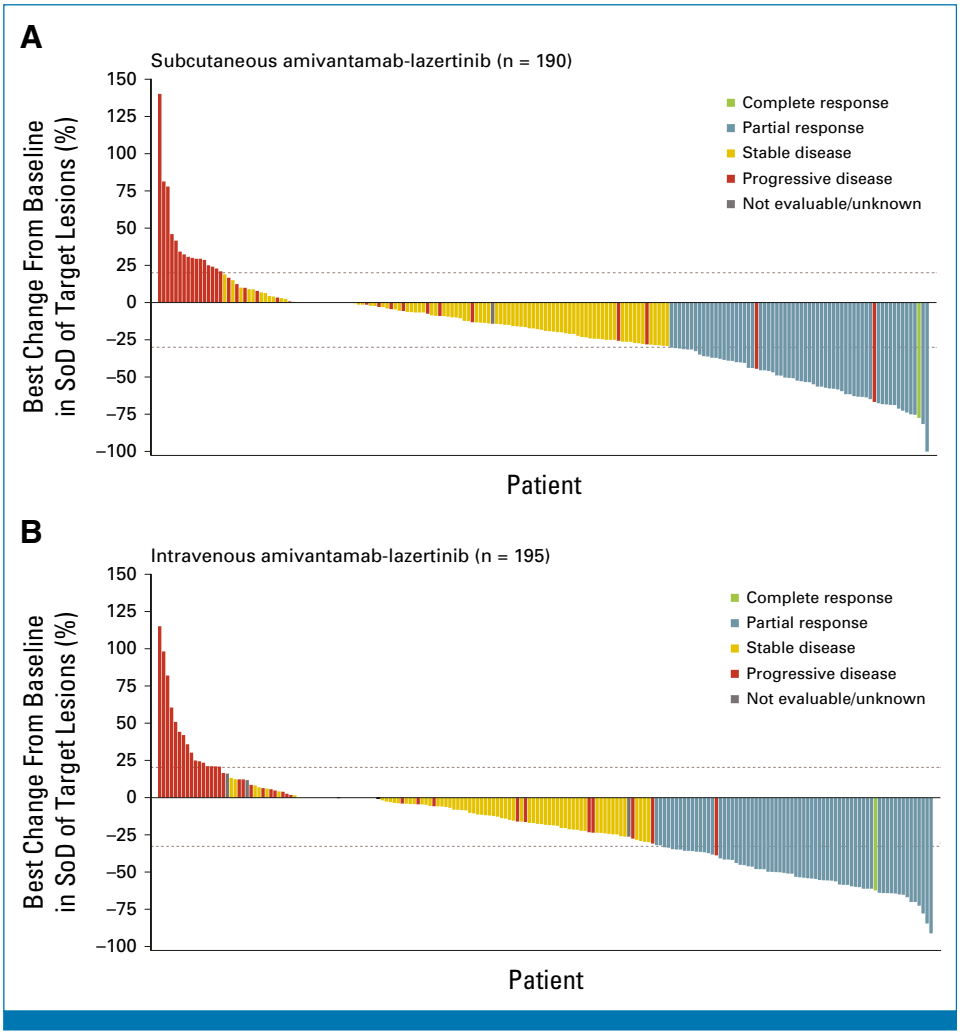

FIG A4. Best percentage change from baseline in target lesions: (A) subcutaneous group and (B) intravenous group. Target lesions were measured as the sum of the longest diameters. The number of patients with measurable disease at baseline was 206 in the subcutaneous group and 212 in the intravenous group; 190 and 195 patients, respectively, had postbaseline tumor assessments. SoD, sum of diameters.

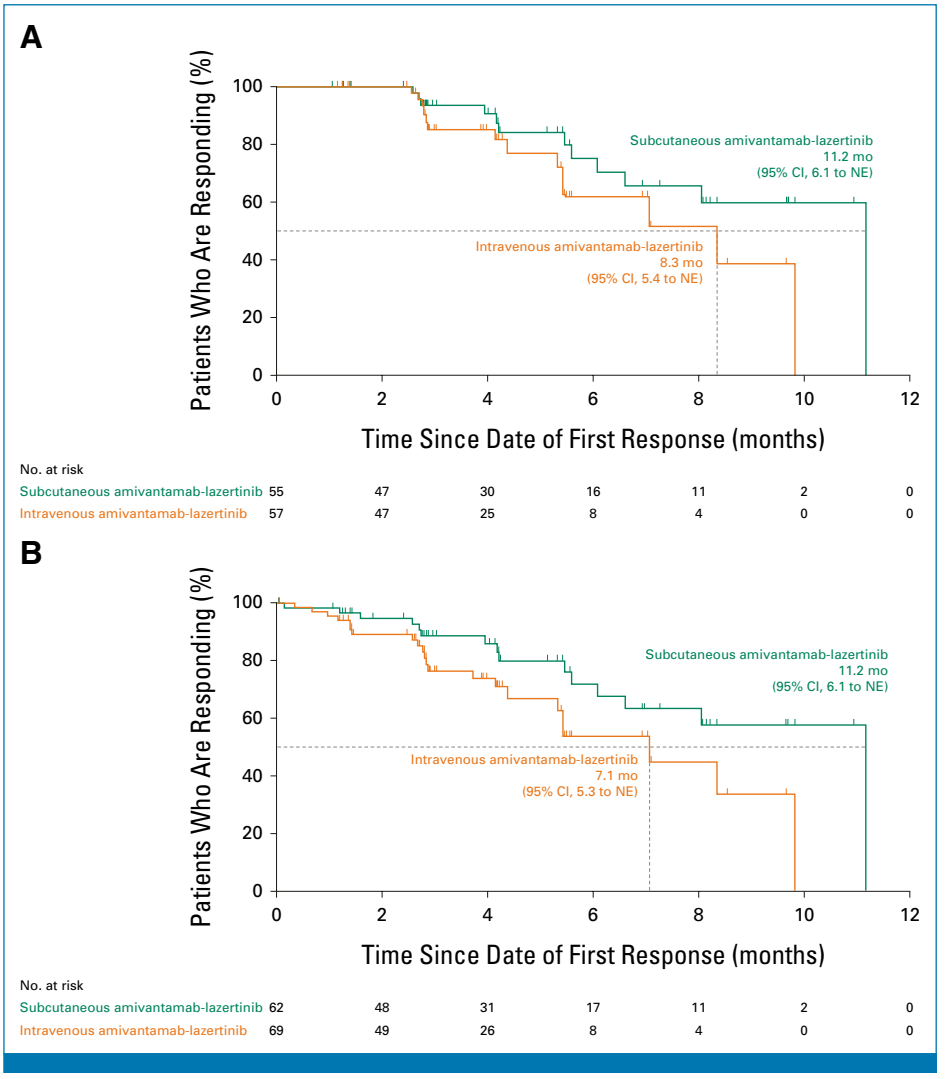

FIG A5. DoR: (A) among confirmed responders and (B) among all responders. The efficacy population included all patients who had undergone random assignment. Included in this analysis were the 55 (confirmed) and 62 (including unconfirmed) responders (of the 206 patients with measurable disease at baseline by RECIST, v1.1) in the subcutaneous group and the 57 (confirmed) and 69 (including unconfirmed) responders (of 212 patients) in the intravenous group, respectively. Tick marks indicate censoring of data. DoR, response duration; NE, not estimable.

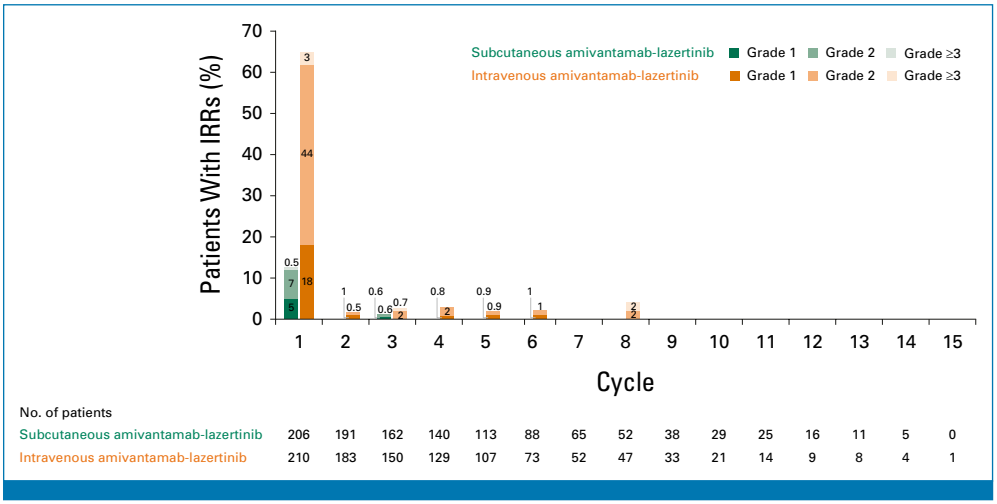

FIG A6. Incidence of IRRs by treatment cycle. IRR was counted only once per time frame per patient, and the event experienced by the patient with the worst toxicity was used. AE, adverse event; IRR, infusion-related reaction.

TABLE A1. Response End Points

End Point	Subcutaneous Group (n = 206)	Intravenous Group (n = 212)
Objective response[a]		
Patients including all responders, % (95% CI)	30 (24 to 37)	33 (26 to 39)
Patients including only confirmed responders, % (95% CI)	27 (21 to 33)	27 (21 to 33)
Best overall response, No. (%)[a]		
Complete response[b]	1 (0.5)	1 (0.5)
Partial response[b]	61 (30)	68 (32)
Stable disease	93 (45)	81 (38)
Progressive disease	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
Disease control rate, % (95% CI)[c]	75 (69 to 81)	71 (64 to 77)
DoR		
Median among all responders, months (95% CI)	11.2 (6.1 to NE)	7.1 (5.3 to NE)
Median among confirmed responders, months (95% CI)	11.2 (6.1 to NE)	8.3 (5.4 to NE)
Time to response		
Median, months (range)	1.5 (1.2-6.9)	1.5 (1.2-9.9)

NOTE. The efficacy population included all the patients who had undergone random assignment.
Abbreviations: DoR, response duration; NE, not estimable.
[a]The objective response (complete or partial response as best response) was assessed using RECIST, v1.1 and analyzed using logistic regression.
[b]Among all responders.
[c]Not protocol-specified; calculated as the sum of complete response, partial response, and stable disease; all responders were included.

TABLE A2. Treatment-Emergent Serious AEs Occurring in at Least Two Patients

Event[a]	Subcutaneous Group (n = 206), No. (%)	Intravenous Group (n = 210), No. (%)
Pneumonitis	9 (4)	6 (3)
COVID-19	4 (2)	4 (2)
Alanine aminotransferase increased	4 (2)	3 (1)
Pneumonia	3 (1)	7 (3)
Interstitial lung disease	3 (1)	1 (0.5)
Fatigue	3 (1)	1 (0.5)
Deep vein thrombosis	2 (1)	4 (2)
Asthenia	2 (1)	2 (1)
Respiratory failure	2 (1)	1 (0.5)
Vomiting	2 (1)	0
Femur fracture	2 (1)	0
Dyspnea	1 (0.5)	2 (1)
Pulmonary embolism	1 (0.5)	2 (1)
Skin infection	1 (0.5)	2 (1)
Aspartate aminotransferase increased	1 (0.5)	2 (1)
Back pain	1 (0.5)	2 (1)
Cerebral infarction	0	3 (1)
Nausea	0	3 (1)
Infusion-related reaction	0	2 (1)
Hypoalbuminemia	0	2 (1)
Rash	0	2 (1)

NOTE. The safety population included all patients who were randomly assigned and received at least one dose of any trial treatment.
[a]Events in this category are listed according to decreasing incidence in the subcutaneous group.

TABLE A3. Venous Thromboembolic Events

Event	Subcutaneous Group (n = 206), No. (%)	Intravenous Group (n = 210), No. (%)
Any venous thromboembolic event	19 (9)	30 (14)
Grade 1	1 (0.5)	7 (3)
Grade 2	16 (8)	16 (8)
Grade 3	2 (1)	6 (3)
Grade 4	0	1 (0.5)
Grade 5	0	0
Any venous thromboembolic event leading to death	0	0
Any venous thromboembolic event leading to discontinuation of any agent	0	2 (1)
Venous thromboembolic events[a]		
Pulmonary embolism	6 (3)	9 (4)
Deep vein thrombosis	5 (2)	11 (5)
Embolism venous	3 (1)	3 (1)
Venous thrombosis limb	3 (1)	3 (1)
Embolism	2 (1)	3 (1)
Thrombosis	2 (1)	1 (0.5)
Subclavian vein thrombosis	1 (0.5)	0
Superficial vein thrombosis	1 (0.5)	0
Pulmonary infarction	0	1 (0.5)
Venous thrombosis	0	3 (1)

NOTE. The safety population included all patients who were randomly assigned and received at least one dose of any trial treatment.
[a]Events in this category are listed according to decreasing incidence in the subcutaneous group.

TABLE A4. Concomitant Anticoagulants

Anticoagulant Use	Subcutaneous Group (n = 206), No. (%)	Intravenous Group (n = 210), No. (%)
Patients with one or more concomitant anticoagulants	164 (80)	171 (81)
Antithrombotic agents		
Direct factor Xa inhibitors	132 (64)	143 (68)
Rivaroxaban	89 (43)	76 (36)
Apixaban	38 (18)	54 (26)
Edoxaban	7 (3)	17 (8)
Heparin group	48 (23)	45 (21)
Enoxaparin	39 (19)	35 (17)
Heparin	4 (2)	2 (1)
Tinzaparin	3 (2)	2 (1)
Low molecular weight heparin	3 (2)	1 (0.5)
Bemiparin	2 (1)	3 (1)
Nadroparin	1 (0.5)	2 (1)
Dalteparin	0	1 (0.5)
Other antithrombotic agents	1 (0.5)	3 (1)
Fondaparinux	1 (0.5)	3 (1)
Direct thrombin inhibitors	0	1 (0.5)
Dabigatran	0	1 (0.5)
Vitamin K antagonists	0	1 (0.5)
Warfarin	0	1 (0.5)

TABLE A5. Venous Thromboembolic and Bleeding Events by Anticoagulation Use and by Treatment Group

Event	Subcutaneous Group (n = 206), No. (%)		Intravenous Group (n = 210), No. (%)	
	Any Prophylactic Anticoagulation (n = 164)	No Prophylactic Anticoagulation (n = 42)	Any Prophylactic Anticoagulation (n = 171)	No Prophylactic Anticoagulation (n = 39)
Any venous thromboembolic event	12 (7)	7 (17)	20 (12)	10 (26)
Grade 1	0	1 (2)	5 (3)	2 (5)
Grade 2	10 (6)	6 (14)	13 (8)	3 (8)
Grade 3 to 4	2 (1)	0	2 (1)	5 (13)
Grade 5	0	0	0	0
Any venous thromboembolic event leading to death	0	0	0	0
Any venous thromboembolic event leading to discontinuation of any agent	0	0	0	2 (5)
Venous thromboembolic events[a]				
Pulmonary embolism	4 (2)	2 (5)	6 (4)	3 (8)
Deep vein thrombosis	3 (2)	2 (5)	8 (5)	3 (8)
Venous embolism	2 (1)	1 (2)	2 (1)	1 (3)
Venous thrombosis limb	3 (2)	0	1 (0.6)	2 (5)
Embolism	1 (0.6)	1 (2)	2 (1)	1 (3)
Thrombosis	1 (0.6)	1 (2)	1 (0.6)	0
Subclavian vein thrombosis	1 (0.6)	0	0	0
Superficial vein thrombosis	0	1 (2)	0	0
Venous thrombosis	0	0	2 (1)	1 (3)
Pulmonary infarction	0	0	0	1 (3)
Any bleeding event	44 (27)	5 (12)	48 (28)	5 (13)
Grade 3 to 4[b]	3 (2)	1 (2)	1 (0.6)	0
Grade 5	0	0	0	0
Any bleeding event leading to death	0	0	0	0
Any bleeding event leading to discontinuation of any agent	1 (0.6)	0	0	0

NOTE. The safety population included all patients who had undergone random assignment and received at least one dose of any trial treatment. The group with any prophylactic anticoagulation included patients who had anticoagulation before or at Cycle 1 Day 1 plus a 3-day window and continued until disease progression, death, withdrawal from the study, occurrence of venous thromboembolism, or Cycle 5 Day 1.

[a]Events in this category are listed according to decreasing incidence in the subcutaneous group.

[b]Grade 3 to 4 events include contusion, gingival bleeding, hemoptysis, hematemesis, and nail bed bleeding.

TABLE A6. Venous Thromboembolic and Bleeding Events by Anticoagulation Use Across All Study Patients

Event	Any Prophylactic Anticoagulation (n = 335), No. (%)	No Prophylactic Anticoagulation (n = 81), No. (%)
Any venous thromboembolic event	32 (10)	17 (21)
Grade 1	5 (1)	3 (4)
Grade 2	23 (7)	9 (11)
Grade 3 to 4	4 (1)	5 (6)
Grade 5	0	0
Any venous thromboembolic event leading to death	0	0
Any venous thromboembolic event leading to discontinuation of any agent	0	2 (2)
Venous thromboembolic events[a]		
Deep vein thrombosis	11 (3)	5 (6)
Pulmonary embolism	10 (3)	5 (6)
Venous thrombosis limb	4 (1)	2 (2)
Venous embolism	4 (1)	2 (2)
Embolism	3 (0.9)	2 (2)
Venous thrombosis	2 (0.6)	1 (1)
Thrombosis	2 (0.6)	1 (1)
Subclavian vein thrombosis	1 (0.3)	0
Pulmonary infarction	0	1 (1)
Superficial vein thrombosis	0	1 (1)
Any bleeding event	92 (27)	10 (12)
Grade 3 to 4[b]	4 (1)	1 (1)
Grade 5	0	0
Any bleeding event leading to death	0	0
Any bleeding event leading to discontinuation of any agent	1 (0.3)	0

NOTE. The safety population included all the patients who were randomly assigned and received at least one dose of any trial treatment. The group with any prophylactic anticoagulation included patients who had anticoagulation before at Cycle 1 Day 1 plus a 3-day window and continued until disease progression, death, withdrawal from the study, occurrence of venous thromboembolism, or Cycle 5 Day 1. The group with no prophylactic anticoagulation included patients who never took prophylactic anticoagulation during the first 4 months of amivantamab and lazertinib combination treatment.

[a]Events in this category are listed according to decreasing incidence in the prophylactic anticoagulation group.

[b]Grade 3 to 4 events include contusion, gingival bleeding, hemoptysis, hematemesis, and nail bed bleeding.

TABLE A7. AEs Leading to Treatment Interruptions, Reductions, and Discontinuations

Event	Subcutaneous Group (n = 206), No. (%)	Intravenous Group (n = 210), No. (%)
Any event leading to interruptions of any study agent	127 (62)	127 (61)
Grade ≥3 events leading to interruptions of any study agent	73 (35)	76 (36)
Most common events leading to interruptions of any study agent[a]		
Paronychia	27 (13)	10 (5)
Dermatitis acneiform	26 (13)	15 (7)
Rash	25 (12)	17 (8)
Increased alanine aminotransferase	10 (5)	8 (4)
COVID-19	9 (4)	12 (6)
Peripheral edema	8 (4)	7 (3)
Hypoalbuminemia	7 (3)	6 (3)
Pyrexia	7 (3)	4 (2)
Increased aspartate aminotransferase	6 (3)	6 (3)
Vomiting	5 (2)	6 (3)
Nausea	4 (2)	10 (5)
Stomatitis	4 (2)	10 (5)
Fatigue	4 (2)	9 (4)
Asthenia	4 (2)	6 (3)
Pneumonia	3 (2)	7 (3)
Hypotension	0	6 (3)
Any event leading to dose reductions of any study agent	63 (31)	52 (25)
Grade ≥3 events leading to dose reductions of any study agent	6 (3)	8 (4)
Most common events leading to dose reductions of any study agent[b]		
Rash	16 (8)	8 (4)
Paronychia	14 (7)	8 (4)
Dermatitis acneiform	12 (6)	9 (4)
Increased alanine aminotransferase	5 (2)	4 (2)
Stomatitis	4 (2)	2 (1)
Diarrhea	4 (2)	0
Fatigue	3 (1)	5 (2)
Hypoalbuminemia	2 (1)	4 (2)
Any event leading to discontinuations of any study agent	26 (13)	29 (14)
Grade ≥3 events leading to discontinuations of any study agent	20 (10)	21 (10)
Most common events leading to discontinuations of any study agent[b]		
Pneumonitis	7 (3)	6 (3)
Dermatitis acneiform	4 (2)	1 (0.5)
Infusion-related reaction	0	4 (2)

NOTE. The safety population included all patients who were randomly assigned and received at least one dose of any trial treatment. Events are listed according to decreasing incidence in the subcutaneous group.

Abbreviation: AE, adverse event.

[a]Listed are AEs that were reported in at least 3% of patients in either group.

[b]Listed are AEs that were reported in at least 2% of patients in either group.

TABLE A8. Treatment-Related AEs

Event	Subcutaneous Group (n = 206), No. (%)		Intravenous Group (n = 210), No. (%)	
Any event	196 (95)		206 (98)	
Grade ≥3	79 (38)		82 (39)	
Any serious event	33 (16)		34 (16)	
Any event resulting in death	3 (1)		4 (2)	
AEs reported in ≥15% of patients in either group[a]	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Paronychia	110 (53)	8 (4)	108 (51)	3 (1)
Rash	90 (44)	8 (4)	91 (43)	8 (4)
Hypoalbuminemia	79 (38)	5 (2)	66 (31)	7 (3)
Dermatitis acneiform	64 (31)	18 (9)	69 (33)	12 (6)
Stomatitis	54 (26)	1 (0.5)	67 (32)	5 (2)
Peripheral edema	46 (22)	4 (2)	43 (20)	1 (0.5)
Nausea	43 (21)	1 (0.5)	40 (19)	3 (1)
Increased alanine aminotransferase	40 (19)	6 (3)	49 (23)	6 (3)
Decreased appetite	37 (18)	1 (0.5)	44 (21)	2 (1)
Diarrhea	36 (17)	3 (1)	31 (15)	2 (1)
Increased aspartate aminotransferase	35 (17)	2 (1)	37 (18)	2 (1)
Vomiting	33 (16)	2 (1)	29 (14)	1 (0.5)
Fatigue	30 (15)	2 (1)	30 (14)	4 (2)
Infusion-related reaction	27 (13)	1 (0.5)	136 (65)	8 (4)

NOTE. The safety population included all patients who were randomly assigned and received at least one dose of any trial treatment.
Abbreviation: AE, adverse event.
[a]Events in this category are listed according to decreasing incidence in the subcutaneous group.

TABLE A9. All Grade 5 AEs

Event[a]	Subcutaneous Group (n = 206), No. (%)	Intravenous Group (n = 210), No. (%)
Pneumonitis	1 (0.5)[b]	3 (1)[b]
Respiratory failure	1 (0.5)[b]	1 (0.5)
Sudden death	1 (0.5)[b]	1 (0.5)
Respiratory disorder	1 (0.5)	0
Pneumonia	1 (0.5)	0
Viral pneumonia	1 (0.5)	0
Cardiac arrest	1 (0.5)	0
Urosepsis	0	1 (0.5)
Asthenia	0	1 (0.5)
Cerebral infarction	0	2 (1)[c]
Acute myocardial infarction	0	1 (0.5)

NOTE. The safety population included all patients who had undergone random assignment and received at least one dose of any trial treatment.

Abbreviation: AE, adverse event.

[a]Events are listed according to decreasing incidence in the subcutaneous group.

[b]All events deemed related to any study treatment.

[c]One event deemed related to any study treatment.

TABLE A10. List of PALOMA-3 Investigators

Principal Investigator	Clinical Site
Hiroaki Akamatsu	Wakayama Medical University Hospital
Mariam Alexander	Medical University of South Carolina
Annalen Bleckmann	University Hospital Münster
Federico Cappuzzo	Istituto Nazionale Tumori Regina Elena
Ying Cheng	Jilin Cancer Hospital
Byoung Chul Cho	Yonsei Cancer Center
Timucin Cil	Adana City Hospital
Alexis Cortot	Institute Coeur Poumon
Pongwut Danchaivijitr	Siriraj Hospital
Till-Oliver Emde	Oncologianova GmbH
Dilek Erdem	Medical Park Samsun Hastanesi
Enriqueta Felip	Vall d'Hebron Institute of Oncology (VIHO)
Fernanda Estevinho	Hospital Pedro Hispano
Maria Lurdes Ferreira	Hospital de Braga
Flavio Ferreira da Silva	Fundacao Pio XII
Maria del Rosario Garcia Campelo	Hospital Universitario A Coruña
Laurent Greillier	Aix Marseille University, APHM, INSERM, CNRS, CRCM, Hôpital Nord
Alastair Greystoke	Newcastle Freeman Hospital
Ji-Youn Han	National Cancer Center
Ping-Chih Hsu	Chang Gung University College of Medicine
Jen-Yu Hung	Kaohsiung Medical University Chung-Ho Memorial Hospital
Mei Ji	The First People's Hospital of Changzhou
Thomas John	Peter MacCallum Cancer Centre
Rohit Joshi	Cancer Research SA
Young-Chul Kim	Chonnam National University Hwasun Hospital
Masashi Kondo	Fujita Health University Hospital
Ernesto Korbenfeld	British Hospital of Buenos Aires—Central British Hospital
Dariusz Kowalski	Maria Sklodowska-Curie National Research Institute of Oncology
Se-Hoon Lee	Samsung Medical Center
Natasha Leighl	Princess Margaret Cancer Centre
Juan Li	Sichuan Cancer Hospital
Sheng-Hao Lin	Changhua Christian Hospital
Baogang Liu	Harbin Medical University Cancer Hospital
Caigang Liu	Shengjing Hospital of China Medical University
John Seng-Hooi Low	Pantai Hospital Kuala Lumpur
Melina E. Marmarelis	Perelman School of Medicine, University of Pennsylvania
Bartomeu Massutí	Alicante University Dr. Balmis Hospital
Anna R. Minchom	The Royal Marsden Hospital and The Institute of Cancer Research
Sara Moore	The Ottawa Hospital Cancer Centre
Mor Moskovitz	Davidoff Cancer Center, Rabin Medical Center
Adnan Nagrial	Westmead Hospital
Danny Nguyen	City of Hope National Medical Center
Silvia Novello	University of Turin, S. Luigi Gonzaga Hospital
Yuichiro Ohe	National Cancer Center Hospital

(continued on following page)

TABLE A10. List of PALOMA-3 Investigators (continued)

Principal Investigator	Clinical Site
Mustafa Özgüroğlu	Istanbul University Cerrahpaşa Medical Faculty
Ozgur Ozyilkan	Adana Baskent University Hospital
Antonio Passaro	European Institute of Oncology, IRCCS
Nir Peled	Shaare Zedek Medical Center
Naiyarat Prasongsook	Phramongkutklao Hospital and Medical College
Angel Qin	University of Michigan Rogel Cancer Center
Elisa F. Ramos	Cetus Oncologia
Joshua K. Sabari	Perlmutter Cancer Center, NYU Langone Health
Jorge Salinas	Cemaic—Centro Privado de Especialidades Medicas Ambulatorias e Investigacion Clinica
Rachel E. Sanborn	Earle A. Chiles Research Institute, Providence Cancer Institute
Mehmet Ali Nahit Sendur	Ankara Yıldırım Beyazıt University, Ankara City Hospital
Felipe José Silva Melo Cruz	Núcleo de Ensino e Pequisa, Instituto Brasileiro de Controle do Câncer
Alexander I. Spira	Virginia Cancer Specialists
Thatthan Suksomboon charoen	Chiang Mai University
Motohiro Tamiya	Osaka International Cancer Institute
Jiunn Liang Tan	University Malaya Medical Centre
Encarnacao Teixeira	Hospital CUF Descobertas
Rajanikar Tota	St John of God Hospital Murdoch
Damien Urban	Chaim Sheba Medical Center
Alain Vergnenègre	CHU de Limoges, Hopital Dupuytren
Pei Jye Voon	Sarawak General Hospital
Vanina Wainsztein	CEMIC (Centro de Educación Médica e Investigaciones Clínicas)
Jialei Wang	Fudan University Shanghai Cancer Center
Thomas Wehler	University Hospital of Giessen and Marburg
James Chih-Hsin Yang	National Taiwan University Cancer Center
Hiroshige Yoshioka	Kansai Medical University Hospital
Alona Zer	Rambam Medical Center
Yanqiu Zhao	The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital
Bogdan Zurawski	Centrum Onkologii im. Prof. F. Lukaszczyka