

a 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

Natasha B. Leigh, MD¹ ; Hiroaki Akamatsu, MD, PhD² ; Sun Min Lim, MD, PhD³ ; Ying Cheng, MD⁴ ; Anna R. Minchom, MD⁵ ; Melina E. Marmarelis, MD⁶ ; Rachel E. Sanborn, MD⁷ ; James Chih-Hsin Yang, MD, PhD⁸ ; Baogang Liu, MD⁹; Thomas John, MD¹⁰ ; Bartomeu Massutí, MD¹¹ ; Alexander I. Spira, MD, PhD¹² ; Se-Hoon Lee, MD, PhD¹³ ; Jialei Wang, MD¹⁴; Juan Li, MD¹⁵ ; Caigang Liu, MD, PhD¹⁶; Silvia Novello, MD, PhD¹⁷ ; Masashi Kondo, MD, PhD¹⁸; Motohiro Tamiya, MD¹⁹; Ernesto Korbenfeld, MD²⁰; Mor Moskovitz, MD²¹; Ji-Youn Han, MD, PhD²² ; Mariam Alexander, MD, PhD²³; Rohit Joshi, MD²⁴ ; Enriqueta Felip, MD, PhD²⁵ ; Pei Jye Voon, MD, MMed²⁶ ; Pongwut Danchaivijitr, MD²⁷ ; Ping-Chih Hsu, MD²⁸ ; Felipe José Silva Melo Cruz, MD²⁹ ; Thomas Wehler, MD, PhD³⁰; Laurent Greillier, MD, PhD³¹ ; Encarnação Teixeira, MD³²; Danny Nguyen, MD³³ ; Joshua K. Sabari, MD³⁴ ; Angel Qin, MD³⁵ ; Dariusz Kowalski, MD, PhD³⁶ ; Mehmet Ali Nahit Şendür, MD, PhD³⁷ ; John Xie, PhD³⁸; Debopriya Ghosh, PhD³⁸; Ali Alhadab, PharmD, PhD³⁹ ; Nahor Haddish-Berhane, PhD⁴⁰ ; Pamela L. Clemens, PhD⁴⁰ ; Patricia Lorenzini, MS⁴⁰; Remy B. Verheijen, PhD⁴¹; Mohamed Gamil, MD⁴⁰; Joshua M. Bauml, MD⁴⁰ ; Mahadi Baig, MD³⁸; and Antonio Passaro, MD, PhD⁴² ; for the PALOMA-3 Investigators

DOI <https://doi.org/10.1200/JCO.24.01001>

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

Accepted June 4, 2024
Published June 10, 2024

J Clin Oncol 42:3593-3605
© 2024 by American Society of Clinical Oncology



View Online Article

Creative Commons Attribution
Non-Commercial No Derivatives
4.0 License

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 $\geq 80\%$ (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 $\geq 60\%$ (on the basis of regulatory precedence from other subcutaneous formulations¹⁷; 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

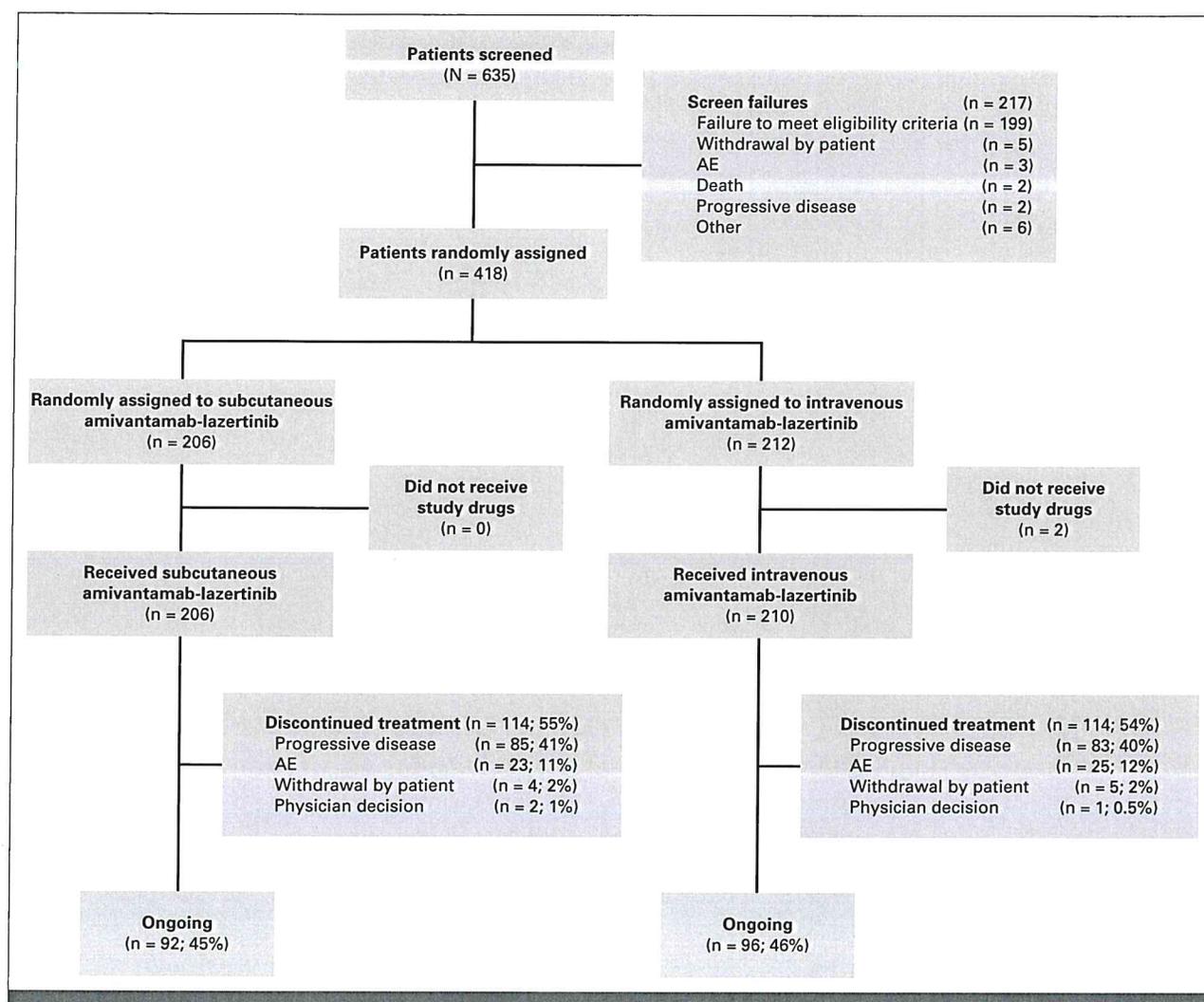


FIG 1. CONSORT diagram of patient disposition. AE, adverse event.

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) $\mu\text{g/mL}$ and 314 (32) $\mu\text{g/mL}$ in the subcutaneous and intravenous groups, respectively; corresponding values at cycle-4-day-1 were 224 (39) $\mu\text{g/mL}$ and 162 (42) $\mu\text{g/mL}$ (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.

^aRussia 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				
<i>C</i> _{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.

^aThe 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.

^bThe objective response (complete or partial response as best response) was assessed by the investigator among all responders.

^cOdds 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).

^dFor 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 anti-amivantamab 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

Downloaded from ascopubs.org by 151.199.248.145 on February 23, 2026 from 151.199.248.145
Copyright © 2026 American Society of Clinical Oncology. All rights reserved.

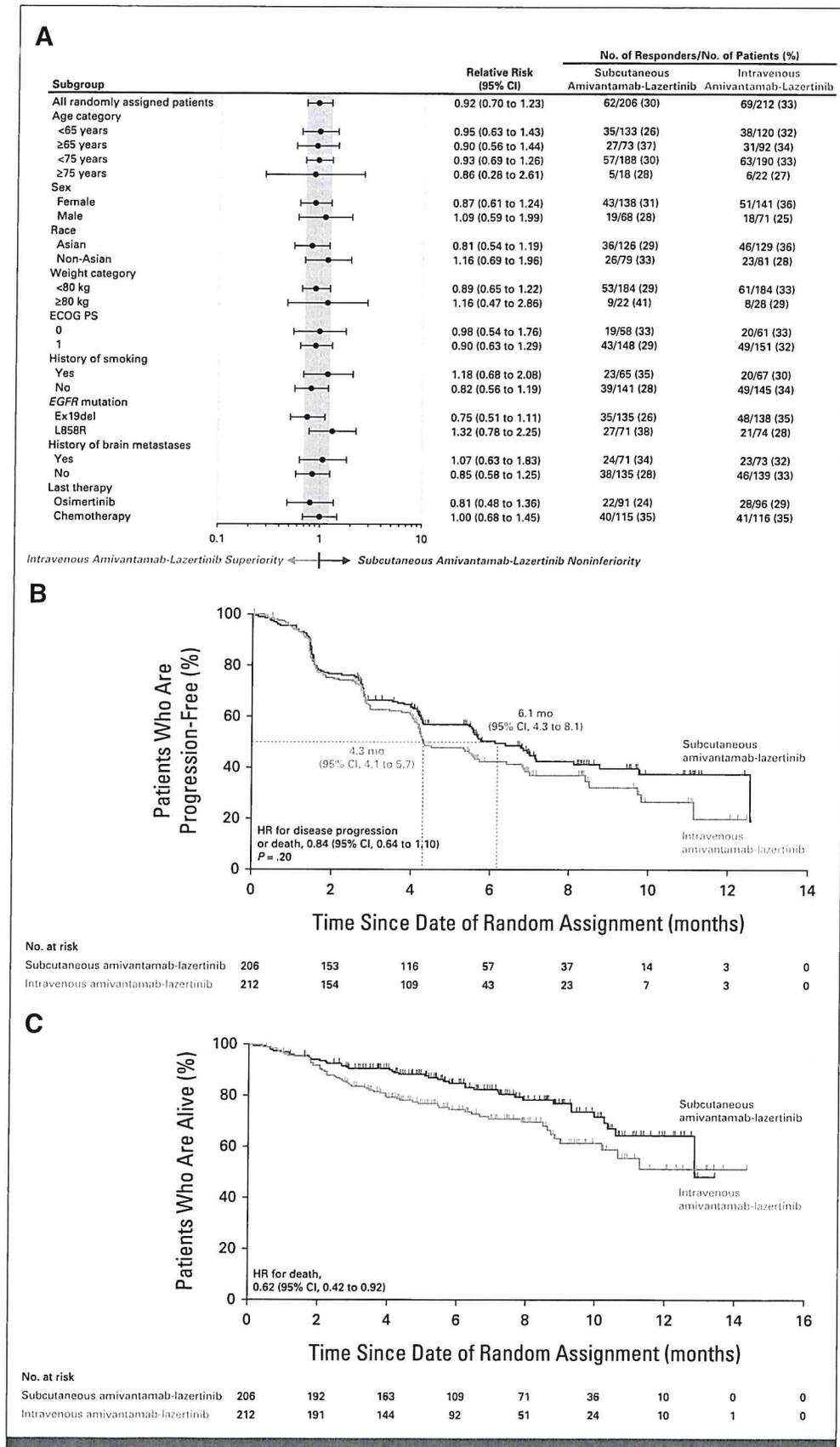


FIG 2. (A) Objective response forest plot, (B) PFS, and (C) OS. The efficacy population included all patients who had undergone random assignment. (A) The shaded area indicates 95% CIs for the (continued on following page)

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 ($\geq 5\%$ in either group) were dermatitis acniform (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 anti-coagulation 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 non-inferior 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 $\geq 15\%$ 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.

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

^bExcluding infusion-/administration-related reactions.

^cEvents 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

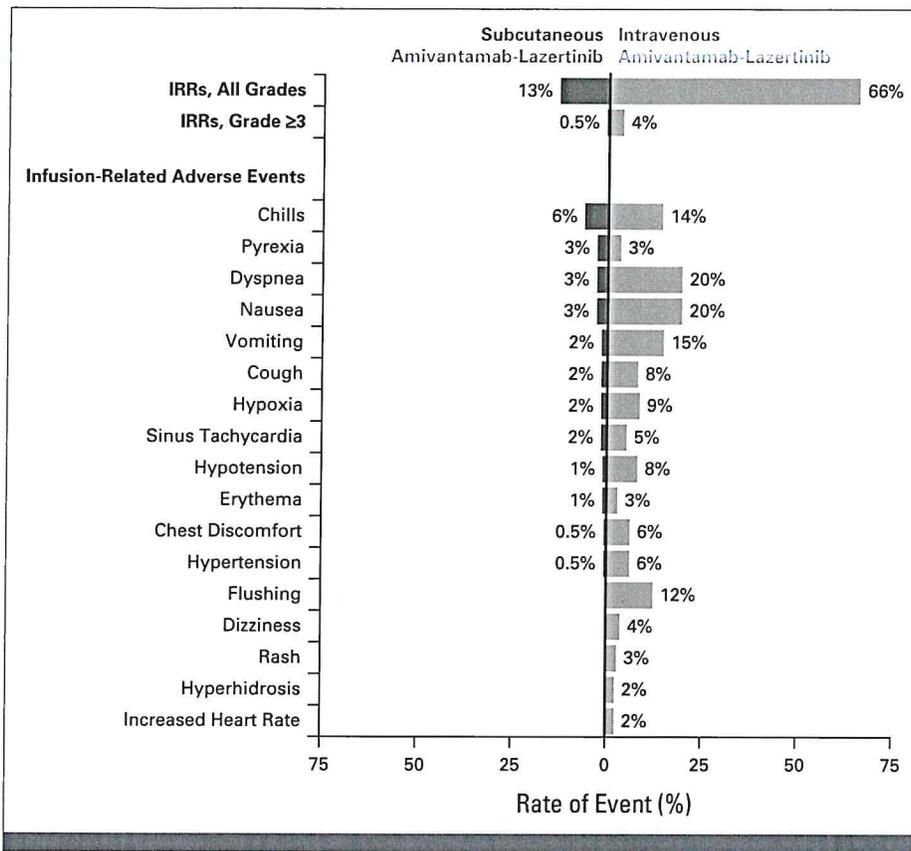


FIG 3. IRRs and infusion-related AEs. The safety population included all patients who had undergone random assignment and received at least one dose of any trial treatment. AE, adverse event; IRR, infusion-related reaction.

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

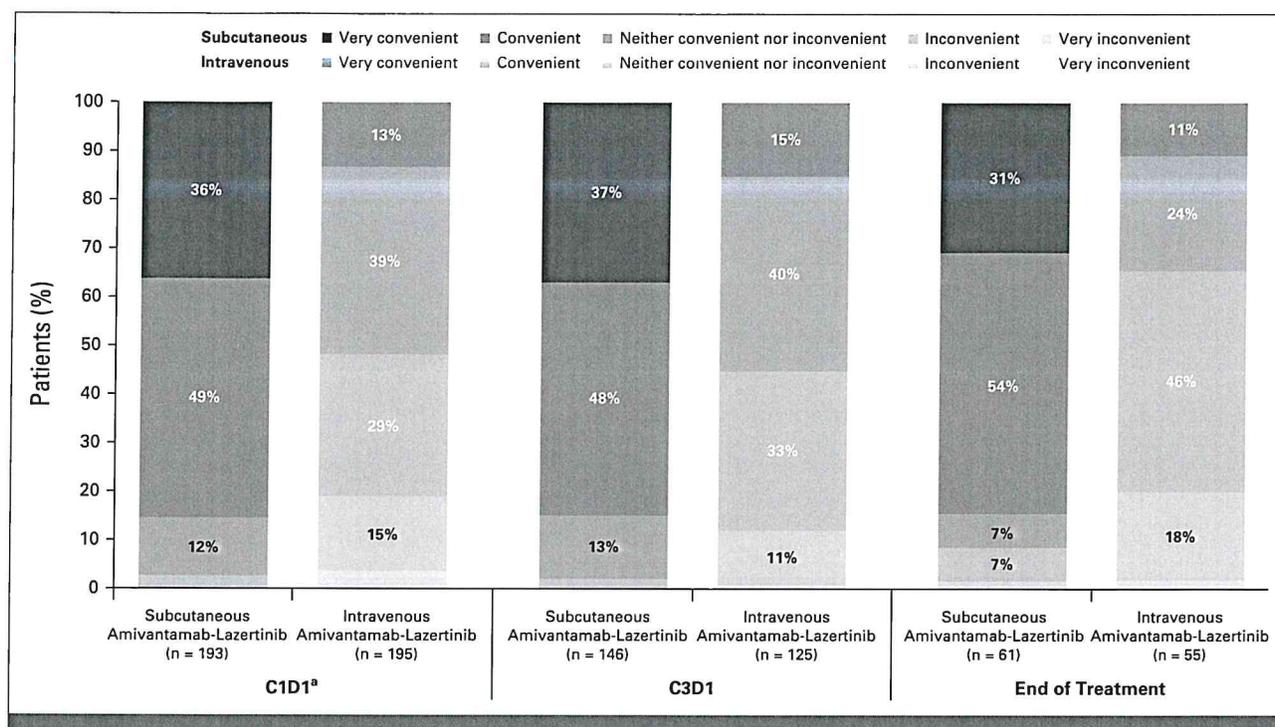


FIG 4. Patient-reported convenience of the subcutaneous injection and intravenous infusion. Item 6 of the modified TASQ asked, “How convenient is it for you to have your [IV infusion/SC injection]?” The modified TASQ was completed by patients after treatment administration in cycle-1 (baseline), cycle-3, and at EOT. EOT data could have been collected after administration of the last dose. ^aC1D2 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.

AFFILIATIONS

¹Princess Margaret Cancer Centre, Toronto, ON, Canada

²Internal Medicine III, Wakayama Medical University, Wakayama, Japan

³Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea

⁴Jilin Cancer Hospital, Changchun, China

⁵Drug Development Unit, The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, United Kingdom

⁶Division of Hematology and Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

⁷Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR

⁸Department of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan

⁹Harbin Medical University Cancer Hospital, Harbin, China

¹⁰Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, VIC, Australia

¹¹Alicante University Dr. Balmis Hospital, ISABIAL, Alicante, Spain

¹²Virginia Cancer Specialists, Fairfax, VA

¹³Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

¹⁴Fudan University Shanghai Cancer Center, Shanghai, China

¹⁵Sichuan Cancer Hospital, Sichuan, China

¹⁶Shengjing Hospital of China Medical University, Shenyang, China

¹⁷Department of Oncology, University of Turin, S. Luigi Gonzaga Hospital, Orbassano (TO), Italy

¹⁸Department of Respiratory Medicine, Fujita Health University School of Medicine, Toyoake, Japan

¹⁹Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan

²⁰British Hospital of Buenos Aires—Central British Hospital, Buenos Aires, Argentina

²¹Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel

²²National Cancer Center, Goyang, Republic of Korea

²³Medical University of South Carolina, Charleston, SC

²⁴Cancer Research SA, Adelaide, SA, Australia

²⁵Medical Oncology Department, Vall d'Hebron Barcelona Hospital Campus, Vall d'Hebron Institute of Oncology (VIHO), Universitat Autònoma de Barcelona, Barcelona, Spain

²⁶Department of Radiotherapy and Oncology, Sarawak General Hospital, Kuching, Malaysia

²⁷Siriraj Hospital, Faculty of Medicine, Mahidol University Bangkok Noi Campus, Bangkok, Thailand

²⁸Department of Thoracic Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

²⁹Núcleo de Ensino e Pesquisa, Instituto Brasileiro de Controle do Câncer, São Paulo, Brazil

³⁰University Hospital of Giessen and Marburg, Giessen and Marburg, Germany

³¹Multidisciplinary Oncology and Therapeutic Innovations Department, Aix Marseille University, APHM, INSERM, CNRS, CRCM, Hôpital Nord, Marseille, France

³²Medical Oncology, Hospital CUF Descobertas, Lisboa, Portugal

³³City of Hope National Medical Center, Duarte, CA

³⁴Perlmutter Cancer Center, New York University Langone Health, New York, NY

³⁵University of Michigan Rogel Cancer Center, Ann Arbor, MI

³⁶Department of Lung Cancer and Thoracic Tumors, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

³⁷Department of Medical Oncology, Ankara Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Turkey

³⁸Janssen Research & Development, Raritan, NJ

³⁹Janssen Research & Development, San Diego, CA

⁴⁰Janssen Research & Development, Spring House, PA

⁴¹Janssen Research & Development, Leiden, the Netherlands

⁴²European Institute of Oncology IRCCS, Milano, Italy

CORRESPONDING AUTHOR

Natasha B. Leighl, MD; e-mail: Natasha.Leighl@uhn.ca.

PRIOR PRESENTATION

Presented at the ASCO Annual Meeting, Chicago, IL, May 31-June 4, 2024.

SUPPORT

Supported by Janssen Research & Development, LLC.

CLINICAL TRIAL INFORMATION

NCT05388669 (PALOMA-3)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.24.01001>.

REFERENCES

- Moore SL, Chiu ML, Bushey BS, et al: A novel bispecific antibody targeting EGFR and cMet is effective against EGFR inhibitor-resistant lung tumors. *Cancer Res* 76:3942-3953, 2016
- Vijayaraghavan S, Lipfert L, Chevalier K, et al: Amivantamab (JNJ-61186372), an Fc enhanced EGFR/cMet bispecific antibody, induces receptor downmodulation and antitumor activity by monocyte/macrophage trogocytosis. *Mol Cancer Ther* 19:2044-2056, 2020
- Yun J, Lee SH, Kim SY, et al: Antitumor activity of amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in diverse models of *EGFR* exon 20 insertion-driven NSCLC. *Cancer Discov* 10:1194-1209, 2020
- Cho BC, Simi A, Sabari J, et al: Amivantamab, an epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) bispecific antibody, designed to enable multiple mechanisms of action and broad clinical applications. *Clin Lung Cancer* 24:89-97, 2023

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI <https://doi.org/10.1200/JCO.24.01001>.

AUTHOR CONTRIBUTIONS

Conception and design: Natasha B. Leighl, Bartomeu Massutí, Alexander I. Spira, Dariusz Kowalski, John Xie, Debopriya Ghosh, Nahor Haddish-Berhane, Remy B. Verheijen, Mohamed Gamil, Joshua M. Bauml

Financial support: Alexander I. Spira, Ali Alhadab

Administrative support: Alexander I. Spira, Jialei Wang, Ali Alhadab
Provision of study materials or patients: Hiroaki Akamatsu, Sun Min Lim, Ying Cheng, Anna R. Minchom, Rachel E. Sanborn, James Chih-Hsin Yang, Thomas John, Bartomeu Massutí, Alexander I. Spira, Jialei Wang, Silvia Novello, Masashi Kondo, Ernesto Korbenfeld, Mor Moskovitz, Ji-Youn Han, Enriqueta Felip, Pei Jye Voon, Ping-Chih Hsu, Felipe José Silva Melo Cruz, Thomas Wehler, Laurent Greillier, Danny Nguyen, Joshua K. Sabari, Ali Alhadab, Mohamed Gamil

Collection and assembly of data: Natasha B. Leighl, Hiroaki Akamatsu, Sun Min Lim, Ying Cheng, Anna R. Minchom, Rachel E. Sanborn, James Chih-Hsin Yang, Baogang Liu, Thomas John, Bartomeu Massutí, Alexander I. Spira, Jialei Wang, Juan Li, Caigang Liu, Masashi Kondo, Motohiro Tamiya, Ernesto Korbenfeld, Mor Moskovitz, Ji-Youn Han, Mariam Alexander, Rohit Joshi, Enriqueta Felip, Pei Jye Voon, Pongwut Danchaivijitr, Ping-Chih Hsu, Felipe José Silva Melo Cruz, Thomas Wehler, Laurent Greillier, Danny Nguyen, Joshua K. Sabari, Angel Qin, Dariusz Kowalski, Mehmet Ali Nahit Şendur, John Xie, Debopriya Ghosh, Ali Alhadab, Remy B. Verheijen, Mohamed Gamil, Joshua M. Bauml, Mahadi Baig, Antonio Passaro

Data analysis and interpretation: Natasha B. Leighl, Hiroaki Akamatsu, Ying Cheng, Anna R. Minchom, Melina E. Marmarelis, Rachel E. Sanborn, James Chih-Hsin Yang, Thomas John, Bartomeu Massutí, Alexander I. Spira, Se-Hoon Lee, Jialei Wang, Silvia Novello, Ernesto Korbenfeld, Mariam Alexander, Rohit Joshi, Enriqueta Felip, Pei Jye Voon, Pongwut Danchaivijitr, Felipe José Silva Melo Cruz, Thomas Wehler, Laurent Greillier, Encarnaçao Teixeira, Danny Nguyen, Joshua K. Sabari, Angel Qin, Dariusz Kowalski, John Xie, Debopriya Ghosh, Ali Alhadab, Nahor Haddish-Berhane, Pamela L. Clemens, Patricia Lorenzini, Remy B. Verheijen, Mohamed Gamil, Joshua M. Bauml, Mahadi Baig, Antonio Passaro

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors thank the patients who participated in the study and their families and caregivers, the physicians and nurses who cared for patients, and the staff members who supported this clinical trial. Medical writing and editorial support were provided by Suparna Abraham, PharmD, of Lumanity Communications Inc and were funded by Janssen Global Services, LLC. A complete list of investigators in the PALOMA-3 trial is provided in the Appendix Table A10.

5. Besse B, Baik CS, Marmarelis ME, et al: Predictive biomarkers for treatment with amivantamab plus lazertinib among *EGFR*-mutated NSCLC in the post-osimertinib setting: Analysis of tissue IHC and ctDNA NGS. *J Clin Oncol* 41:9013, 2023
6. RYBREVANT (Amivantamab-vmjw) Injection, for Intravenous Use [prescribing Information]. Horsham, PA: Janssen Biotech, 2024
7. Cho BC, Lu S, Filip E, et al: Amivantamab plus lazertinib in previously untreated *EGFR*-mutated advanced NSCLC. *N Engl J Med* 10.1056/NEJMoa2403614 [epub ahead of print June 26, 2024]
8. Park K, Sabari JK, Haura EB, et al: Management of infusion-related reactions (IRRs) in patients receiving amivantamab in the CHRYSALIS study. *Lung Cancer* 178:166-171, 2023
9. Minchom A, Krebs MG, Cho BC, et al: Subcutaneous amivantamab in patients with advanced solid malignancies: The PALOMA study—updated safety and confirmation of the recommended phase 2 dose. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, June 2-6, 2023
10. Leigh N, Cho BC, Hiet S, et al: Amivantamab in patients with advanced NSCLC and MET exon14 skipping mutation: Results from the CHRYSALIS study. Presented at IASLC 2023 World Conference on Lung Cancer, Singapore, September 9-12, 2023
11. Passaro A, Wang J, Shah S, et al: Letter to the editor regarding 'Correspondence to: 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' by Moik F, Riedl JM, and Ay C. *Ann Oncol* 35:328-329, 2024
12. Passaro A, Wang J, Wang Y, et al: 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. *Ann Oncol* 35:77-90, 2024
13. Zhou C, Tang KJ, Cho BC, et al: Amivantamab plus chemotherapy in NSCLC with *EGFR* exon 20 insertions. *N Engl J Med* 389:2039-2051, 2023
14. Girard N, Cho BC, Spira AI, et al: Risk factors for venous thromboembolism (VTE) among patients with *EGFR*-mutated advanced non-small cell lung cancer (NSCLC) receiving amivantamab plus lazertinib versus either agent alone. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, June 2-6, 2023
15. European Medicines Agency: Concept paper for the development of a guideline on non-inferiority and equivalence comparisons in clinical trials. https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-development-guideline-non-inferiority-equivalence-comparisons-clinical-trials_en.pdf
16. U.S. Food and Drug Administration: Non-inferiority clinical trials to establish effectiveness. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials>
17. Mateos MV, Nahi H, Legiec W, et al: Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): A multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol* 7:e370-e380, 2020
18. Haddish-Berhane N, Su Y, Russu A, et al: Determination and confirmation of recommended Ph2 dose of amivantamab in epidermal growth factor receptor exon 20 insertion non-small cell lung cancer. *Clin Pharmacol Ther* 115:468-477, 2024
19. Feeney OM, Gracia G, Brundel DHS, et al: Lymph-directed immunotherapy—Harnessing endogenous lymphatic distribution pathways for enhanced therapeutic outcomes in cancer. *Adv Drug Deliv Rev* 160:115-135, 2020
20. Trevasikis NL, Kaminskas LM, Porter CJ: From sewer to saviour—Targeting the lymphatic system to promote drug exposure and activity. *Nat Rev Drug Discov* 14:781-803, 2015
21. Styles IK, Feeney OM, Nguyen TH, et al: Removal of interstitial hyaluronan with recombinant human hyaluronidase improves the systemic and lymphatic uptake of cetuximab in rats. *J Control Release* 315:85-96, 2019
22. Cho BC, Filip E, Spira A, et al: Amivantamab plus lazertinib versus osimertinib as first-line treatment in *EGFR*-mutated advanced NSCLC. Presented at European Society for Medical Oncology (ESMO) Congress, Madrid, Spain, October 20-24, 2023
23. Khorana AA, Palaia J, Rosenblatt L, et al: Venous thromboembolism incidence and risk factors associated with immune checkpoint inhibitors among patients with advanced non-small cell lung cancer. *J Immunother Cancer* 11:e006072, 2023
24. Mulder FI, Horváth-Puhó E, van Es N, et al: Venous thromboembolism in cancer patients: A population-based cohort study. *Blood* 137:1959-1969, 2021
25. Khorana AA, Soff GA, Kakkar AK, et al: Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med* 380:720-728, 2019
26. Leigh NB, Minchom AR, Lee KH, et al: Subcutaneous amivantamab administered every 4 weeks (Q4W) in patients with advanced solid malignancies: The phase Ib PALOMA study (ID 369). Presented at European Lung Cancer Congress (ELCC), Prague, Czech Republic, March 20-23, 2024

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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Natasha B. Leighl

Honoraria: BeiGene, Bristol Myers Squibb, Janssen, MSD Oncology, Takeda

Research Funding: MSD (Inst), Lilly (Inst), AstraZeneca Canada (Inst), Inivata/NeoGenomics (Inst), Janssen Oncology (Inst), Novartis (Inst), Pfizer (Inst)

Travel, Accommodations, Expenses: AstraZeneca

Hiroaki Akamatsu

Honoraria: AstraZeneca, Lilly, Pfizer, MSD, Bristol Myers Squibb Japan, Taiho Pharmaceutical, Chugai Pharma, Boehringer Ingelheim, Ono Pharmaceutical, Amgen, Nippon Kayaku, Novartis, Takeda

Consulting or Advisory Role: Amgen, Janssen, Sandoz

Research Funding: Amgen (Inst), Chugai Pharma (Inst)

Sun Min Lim

Honoraria: Takeda, Boehringer Ingelheim, Yuhan

Research Funding: Janssen Research & Development

Anna R. Minchom

Honoraria: Janssen, Merck, GSK, Seagen

Consulting or Advisory Role: Janssen Oncology, Faron Pharmaceuticals, GSK, MSD, Immuteq, Genmab, Merck

Research Funding: Merck (Inst), MSD Oncology (Inst), Astex Pharmaceuticals (Inst)

Travel, Accommodations, Expenses: Janssen Oncology, Amgen

Melina E. Marmarelis

Stock and Other Ownership Interests: Merck, Johnson & Johnson

Honoraria: Novocure, AstraZeneca, Janssen Oncology, Takeda, Blueprint Medicines, Thermo Fisher Scientific

Consulting or Advisory Role: AstraZeneca, Ikena Oncology, Bristol Myers Squibb/Celgene, AstraZeneca, Janssen Oncology, Regeneron

Research Funding: Lilly (Inst), AstraZeneca (Inst), Janssen Oncology (Inst), Ikena Oncology (Inst), Genentech (Inst), Merck (Inst)

Travel, Accommodations, Expenses: Regeneron

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/856967>

Rachel E. Sanborn

Honoraria: MJH Life Sciences, Targeted Oncology, Curio Science, Illumina

Consulting or Advisory Role: AstraZeneca, EMD Serono, Janssen Oncology, MacroGenics, Sanofi/Aventis, Regeneron, GSK, Illumina, G1 Therapeutics, Daiichi Sankyo, Lilly, Amgen, Gilead Sciences, GE Healthcare

Research Funding: Bristol Myers Squibb (Inst), Merck, AstraZeneca

James Chih-Hsin Yang

Honoraria: Boehringer Ingelheim, Roche, MSD, AstraZeneca, Novartis, Bristol Myers Squibb, Ono Pharmaceutical, Takeda, Lilly, Pfizer, Amgen

(Inst), AstraZeneca/MedImmune (Inst), Boehringer Ingelheim (Inst), Dizal Pharma (Inst), Taiho Pharmaceutical (Inst), Pfizer (Inst), Takeda (Inst), Roche/Genentech (Inst), Daiichi Sankyo/AstraZeneca (Inst), MSD Oncology (Inst), BeiGene (Inst), Gilead Sciences (Inst), Sanofi/Regeneron (Inst)

Consulting or Advisory Role: Boehringer Ingelheim, Novartis, AstraZeneca, Clovis Oncology, Lilly (Inst), MSD Oncology, Celgene, Bayer, Pfizer, Ono Pharmaceutical, Bristol Myers Squibb, Boehringer Ingelheim (Inst), Yuhan, Hansoh, Blueprint Medicines, Daiichi Sankyo, G1 Therapeutics, AbbVie, Takeda, Amgen, Incyte, GSK (Inst), Amgen (Inst), Takeda (Inst), AstraZeneca (Inst), Novartis (Inst), MSD Oncology (Inst), Janssen Oncology (Inst), Merck KGaA (Inst), Daiichi Sankyo/AstraZeneca (Inst), Puma Biotechnology (Inst), Gilead Sciences (Inst), Pfizer (Inst), Taiho Pharmaceutical (Inst), Bayer (Inst), Roche/Genentech (Inst), Sanofi (Inst)

Research Funding: AstraZeneca (Inst)

Travel, Accommodations, Expenses: Pfizer

Thomas John

Honoraria: AstraZeneca/MedImmune, Roche/Genentech, Bristol Myers Squibb, MSD Oncology

Consulting or Advisory Role: AstraZeneca, Pfizer, AstraZeneca/MedImmune, Roche/Genentech, Ignyta, Boehringer Ingelheim, Novartis, MSD Oncology, Merck KGaA, Bristol Myers Squibb, Amgen (Inst), PharmaMar (Inst), Specialised Therapeutics, Gilead Sciences, Seagen (Inst)

Travel, Accommodations, Expenses: Boehringer Ingelheim, Roche, AstraZeneca, Bristol Myers Squibb, Roche, MSD

Bartomeu Massutí

Consulting or Advisory Role: Roche, AstraZeneca, Janssen, Amgen

Speakers' Bureau: Roche, AstraZeneca, Bristol Myers Squibb, Janssen Oncology, Pfizer, MSD Oncology

Travel, Accommodations, Expenses: Roche, MSD Oncology, AstraZeneca, Pfizer

Alexander I. Spira

Leadership: Next Oncology (Inst)

Honoraria: CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen Oncology, Novartis, Bristol Myers Squibb, Bayer, Prelude Therapeutics, AbbVie, Astellas Pharma

Consulting or Advisory Role: Incyte, Amgen, Novartis, AstraZeneca/MedImmune (Inst), Mirati Therapeutics, Gritstone Bio, Jazz Pharmaceuticals, Merck (Inst), Bristol Myers Squibb (Inst), Takeda, Janssen Research & Development, Mersana, Blueprint Medicines (Inst), Gritstone Bio, Daiichi Sankyo/AstraZeneca, Regeneron, Lilly, Black Diamond Therapeutics, Sanofi, ArriVent Biopharma

Research Funding: Roche (Inst), AstraZeneca (Inst), Boehringer Ingelheim (Inst), Astellas Pharma (Inst), MedImmune (Inst), Novartis (Inst), Incyte (Inst), AbbVie (Inst), Ignyta (Inst), Takeda (Inst),

MacroGenics (Inst), CytomX Therapeutics (Inst), LAM Therapeutics, Astex Pharmaceuticals (Inst), Bristol Myers Squibb (Inst), Loxo (Inst), Gritstone Bio (Inst), Plexikon (Inst), Amgen (Inst), Loxo (Inst), Daiichi Sankyo (Inst), ADC Therapeutics (Inst), Janssen Oncology (Inst), ADC Therapeutics (Inst), Rubius Therapeutics (Inst), SyntheKine (Inst), Mersana (Inst), Blueprint Medicines (Inst), Regeneron (Inst), Alkermes (Inst), Revolution Medicines (Inst), Medikine (Inst), Black Diamond Therapeutics (Inst), BluPrint Oncology (Inst), Nalo Therapeutics (Inst), Scorpion Therapeutics (Inst), ArriVent Biopharma (Inst), Revolution Medicines (Inst), Prelude Therapeutics (Inst)

Se-Hoon Lee

Honoraria: AstraZeneca/MedImmune, Roche, Lilly, Amgen, Yuhan, MSD
Consulting or Advisory Role: AstraZeneca, Roche, Pfizer, Lilly, Bristol Myers Squibb/Ono, Takeda, Janssen, IMBdx, Abion, BeiGene, Daiichi Sankyo, ImmuneOncia, Merck (German), MSD, Novartis
Speakers' Bureau: Abion
Research Funding: AstraZeneca (Inst), Lunit (Inst), MSD (Inst)

Silvia Novello

Consulting or Advisory Role: Sanofi
Speakers' Bureau: AstraZeneca, MSD, Bristol Myers Squibb, Roche, Pfizer, Lilly, Takeda, AbbVie, Boehringer Ingelheim, Bayer, Amgen, BeiGene, Novartis, Janssen
Travel, Accommodations, Expenses: Sanofi

Masashi Kondo

Honoraria: Chugai Pharma, Lilly, Pfizer, AstraZeneca, Ono Pharmaceutical, Bristol Myers Squibb, MSD K.K, Takeda, Pfizer
Speakers' Bureau: Chugai Pharma, Lilly, AstraZeneca, Ono Pharmaceutical, Bristol Myers Squibb, MSD, Takeda, Daiichi Sankyo Healthcare
Research Funding: Chugai Pharma (Inst), Ono Pharmaceutical (Inst), AstraZeneca (Inst), MSD (Inst), Takeda (Inst)

Motohiro Tamiya

Honoraria: Boehringer Ingelheim, Chugai Pharma, AstraZeneca, Taiho Pharmaceutical, Lilly Japan, Asahi Kasei, MSD, Ono Pharmaceutical, Bristol Myers Squibb Japan, Amgen, Takeda, Pfizer, Novartis, Nihonkayaku, Kyowa Kirin International, Bayer
Consulting or Advisory Role: Pfizer
Research Funding: Boehringer Ingelheim, Ono Pharmaceutical, MSD

Ernesto Korbenfeld

Honoraria: AstraZeneca
Consulting or Advisory Role: Pfizer

Mor Moskovitz

Honoraria: MSD, Bristol Myers Squibb, Roche, Takeda, AbbVie, AstraZeneca, Johnson & Johnson/Janssen
Consulting or Advisory Role: AstraZeneca, MSD Oncology, Takeda, Roche, Pfizer, Johnson & Johnson, Novartis, Amgen
Travel, Accommodations, Expenses: Pfizer, MSD, Roche

Ji-Youn Han

Honoraria: AstraZeneca, Takeda, Novartis, Merck, Janssen, Pfizer, Yuhan
Consulting or Advisory Role: Novartis, Merck, Takeda, Janssen, Lantern Pharma, Amgen, AstraZeneca, Daiichi Sankyo/UCB Japan, Oncovix, AbbVie
Research Funding: Roche, Pfizer

Mariam Alexander

Consulting or Advisory Role: Amgen

Rohit Joshi

Honoraria: Bristol Myers Squibb, MSD, Roche, Pfizer, Pfizer/EMD Serono, Ipsen, Gilead Sciences
Consulting or Advisory Role: MSD, AstraZeneca
Speakers' Bureau: Gilead Sciences
Travel, Accommodations, Expenses: Novartis

Enriqueta Felip

Consulting or Advisory Role: AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Lilly, Roche, Gilead Sciences, GSK, Janssen, Merck Serono, MSD, Novartis, Peptomyc, Pfizer, Regeneron, Sanofi, Takeda, Genmab
Speakers' Bureau: Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Lilly, Roche, Genentech, Janssen, Medical Trends, Medscape, Merck Serono, MSD, PeerVoice, Pfizer, Sanofi, Takeda, Touch Oncology
Travel, Accommodations, Expenses: AstraZeneca, Janssen, Roche
Other Relationship: Grifols
Uncompensated Relationships: Member of the Scientific Advisory Committee -Hospital Universitari Parc Taulí, SEOM (Sociedad Española de Oncología Médica), President from 2021-2023, "ETOP IBCSG Partners" Member of the Scientific Committee

Pei Jye Voon

Consulting or Advisory Role: AstraZeneca, Ipsen, MSD, Novartis, Pfizer, BeiGene, Amgen
Research Funding: Novartis (Inst), Boehringer Ingelheim (Inst), Viracta Therapeutics (Inst), Roche (Inst), Merck KGaA (Inst), MSD (Inst), BeiGene (Inst), AstraZeneca (Inst), Janssen-Cilag (Inst), Johnson & Johnson (Inst)

Pongwut Danchaivijitr

Consulting or Advisory Role: Merck, AstraZeneca, Pfizer, Roche, Janssen Oncology
Speakers' Bureau: Merck, AstraZeneca, Pfizer, Roche, Janssen Oncology
Research Funding: Merck (Inst), Roche (Inst), AstraZeneca (Inst), Daiichi Sankyo/AstraZeneca (Inst), Boehringer Ingelheim (Inst)

Felipe José Silva Melo Cruz

Consulting or Advisory Role: Pfizer, Bayer, Astellas Pharma, Janssen
Travel, Accommodations, Expenses: Janssen Oncology, Novartis

Thomas Wehler

Honoraria: Roche/Genentech, Boehringer Ingelheim, MSD, Bristol Myers Squibb, Pfizer, AstraZeneca, Janssen, Novocure
Consulting or Advisory Role: AstraZeneca, Roche/Genentech, Pfizer, MSD, Bristol Myers Squibb, AbbVie, Merck Serono, Boehringer Ingelheim
Research Funding: AstraZeneca, Roche/Genentech, Boehringer Ingelheim
Travel, Accommodations, Expenses: Pfizer, Celgene, Roche/Genentech, Boehringer Ingelheim, AstraZeneca, Janssen

Laurent Greillier

Honoraria: AstraZeneca, Roche, Bristol Myers Squibb, MSD, Takeda, Novartis, Pfizer, Sanofi, Amgen, Janssen
Consulting or Advisory Role: Roche, Bristol Myers Squibb, Takeda, MSD, AstraZeneca, Novartis, Janssen
Travel, Accommodations, Expenses: Roche, MSD, Bristol Myers Squibb, AstraZeneca, Pfizer, Amgen

Encarnação Teixeira

Consulting or Advisory Role: AstraZeneca, Janssen Oncology, Lilly, Takeda, Roche, MSD, Merck Serono
Speakers' Bureau: MSD Oncology, Sanofi/Aventis, Merck Serono, Janssen

Danny Nguyen

Stock and Other Ownership Interests: Intuitive Surgical (I), Teladoc (I)
Consulting or Advisory Role: Janssen Oncology
Other Relationship: Takeda, Novartis, Seagen, Pfizer
Uncompensated Relationships: Takeda, Novartis

Joshua K. Sabari

Consulting or Advisory Role: AstraZeneca, Pfizer, Regeneron, Medscape, Takeda, Janssen, Genentech/Roche, Mirati Therapeutics, AbbVie, Loxo/Lilly, Sanofi, Janssen (Inst), Loxo/Lilly (Inst), Mirati Therapeutics (Inst), Regeneron (Inst)

Angel Qin

Consulting or Advisory Role: Summit Therapeutics, Regeneron, Strata Oncology, Janssen
Research Funding: AstraZeneca (Inst), Roche (Inst), Janssen Oncology (Inst)

Dariusz Kowalski

Consulting or Advisory Role: Bristol Myers Squibb, Boehringer Ingelheim, Merck Serono, Roche/Genentech, AstraZeneca, MSD, Pfizer, Amgen, Johnson & Johnson/Janssen, Takeda, Sanofi/Aventis

Mehmet Ali Nahit Şendur

Honoraria: Amgen, Bristol Myers Squibb, MSD, Pfizer, Roche, Bayer, Novartis, Janssen, Astellas Pharma, Takeda
Speakers' Bureau: Bristol Myers Squibb, Pfizer, Amgen, Novartis, Roche, Janssen, Astellas Pharma, Takeda, Abdi Ibrahim

John Xie

Employment: Johnson & Johnson
Stock and Other Ownership Interests: Johnson & Johnson

Debopriya Ghosh

Employment: Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen
Travel, Accommodations, Expenses: Johnson & Johnson/Janssen

Ali Alhadab

Employment: Pfizer, Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Pfizer, Johnson & Johnson/Janssen
Travel, Accommodations, Expenses: Johnson & Johnson/Janssen

Nahor Haddish-Berhane

Employment: Johnson and Johnson
Stock and Other Ownership Interests: Johnson and Johnson

Pamela L. Clemens

Employment: Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen

Patricia Lorenzini

Employment: Johnson & Johnson/Janssen

Remy B. Verheijen

Employment: AstraZeneca, Johnson & Johnson
Stock and Other Ownership Interests: AstraZeneca, Johnson & Johnson, Aduro Biotech, Chinook Tx, Galapagos NV

Mohamed Gamil

Employment: Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen
Travel, Accommodations, Expenses: Johnson & Johnson/Janssen

Joshua M. Bauml

Employment: Janssen Research & Development
Stock and Other Ownership Interests: Janssen Research & Development

Mahadi Baig

Employment: Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen

Antonio Passaro

Consulting or Advisory Role: Roche/Genentech, Bristol Myers Squibb, AstraZeneca, MSD Oncology, Pfizer, Boehringer Ingelheim, Johnson & Johnson/Janssen, Novartis, Daiichi Sankyo Europe GmbH, Bayer
Speakers' Bureau: AstraZeneca, Johnson & Johnson/Janssen, Daiichi Sankyo Europe GmbH, MSD Oncology

No other potential conflicts of interest were reported.

APPENDIX

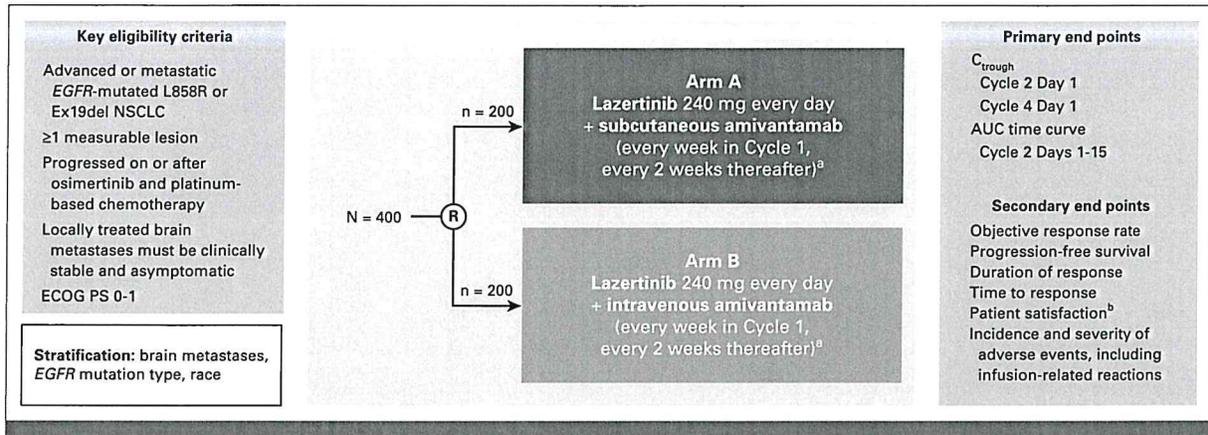


FIG A1. PALOMA-3 study design. ^aCycle 1 for intravenous amivantamab-lazertinib: Days 1, 2 (Day 2 applies to intravenous split dose only), 8, 15, and 22; Cycle 1 for subcutaneous amivantamab-lazertinib: Days 1, 8, 15, and 22; after Cycle 1 for all: Days 1, 15 (28-day cycles). Subcutaneous amivantamab is coformulated with recombinant human hyaluronidase. ^bAssessed 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.

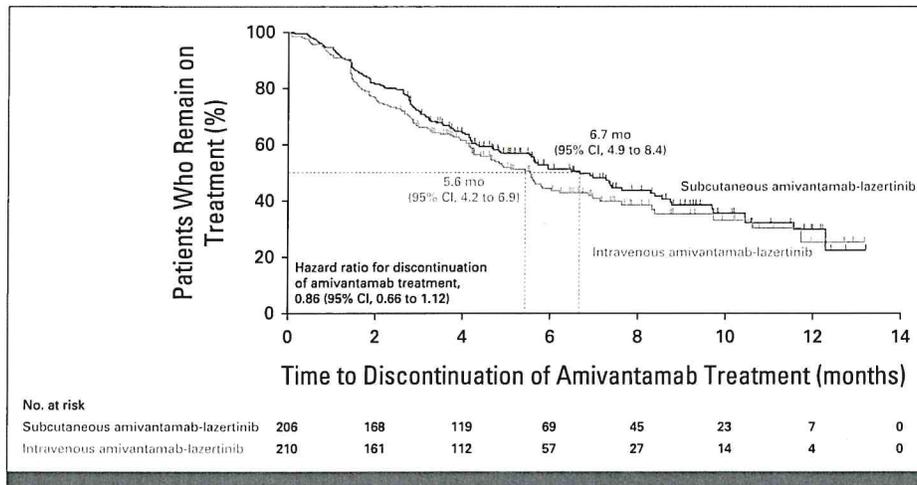


FIG A2. Time to amivantamab discontinuation. The dashed lines indicate the median time to amivantamab discontinuation in the two groups, and the tick marks indicate censoring of data.

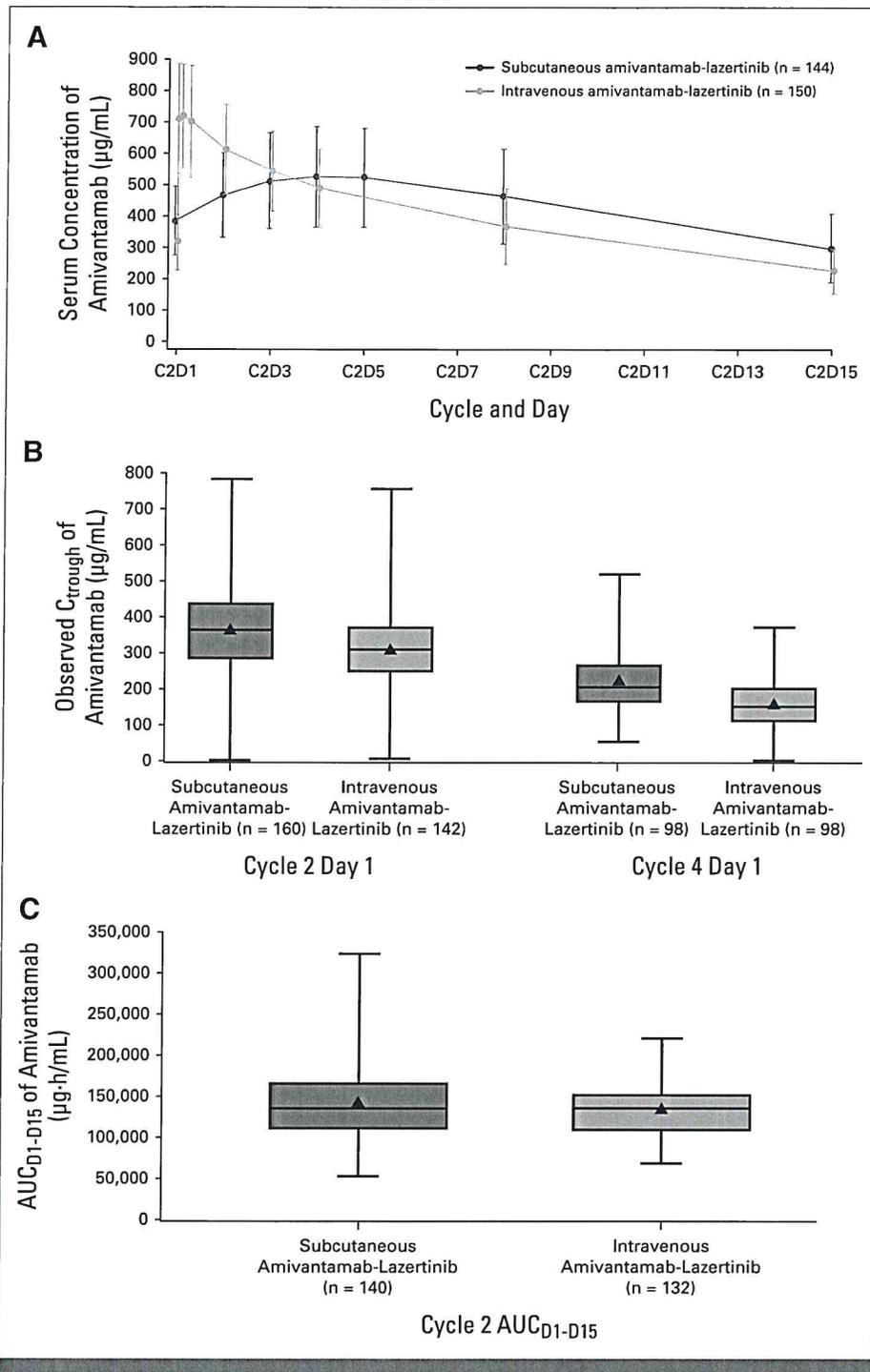


FIG A3. (A) Observed concentration-time profiles, (B) C_{trough} , and (C) $\text{AUC}_{\text{D1-D15}}$ of amivantamab. To capture the peak concentration of intravenous amivantamab, two samples were analyzed soon after the end of infusion (at 10 minutes and 2 hours after intravenous infusion). The upper 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; $\text{AUC}_{\text{D1-D15}}$, AUC between Cycle 2 Day 1 and Day 15; C, Cycle; C_{trough} , observed serum concentration of amivantamab at steady state; D, Day.

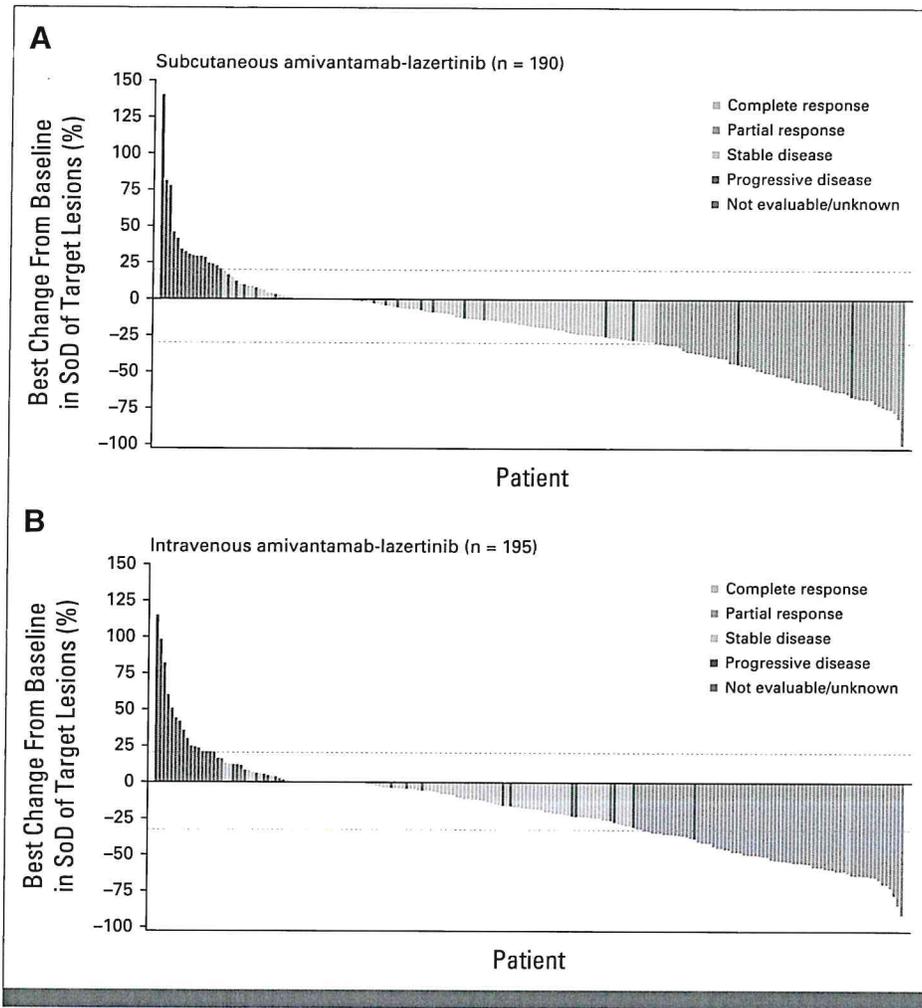


FIG A4. Best percentage change from baseline in target lesions: (A) subcutaneous group and (B) intravenous group. Target lesions were measured as the sum of the longest diameters. The number of patients with measurable disease at baseline was 206 in the subcutaneous group and 212 in the intravenous group;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

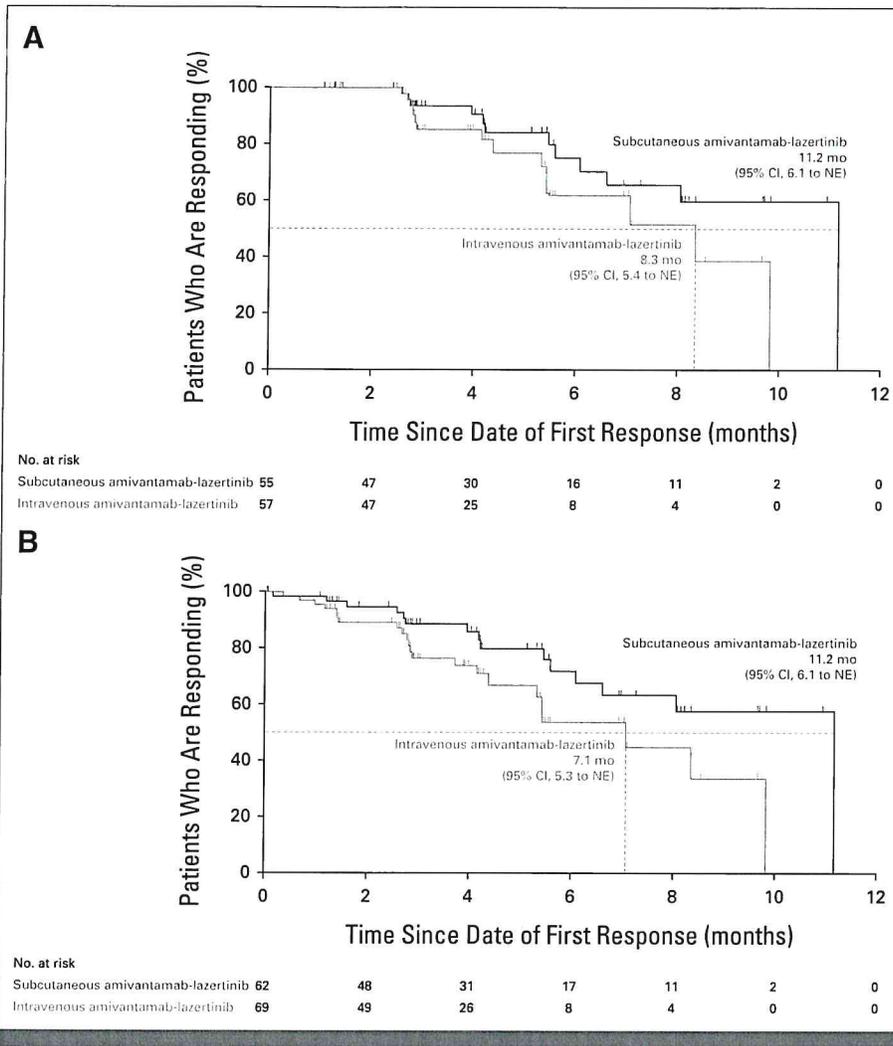


FIG A5. DoR: (A) among confirmed responders and (B) among all responders. The efficacy population included all patients who had undergone random assignment. Included in this analysis were the 55 (confirmed) and 62 (including unconfirmed) responders (of the 206 patients with measurable disease at baseline 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.

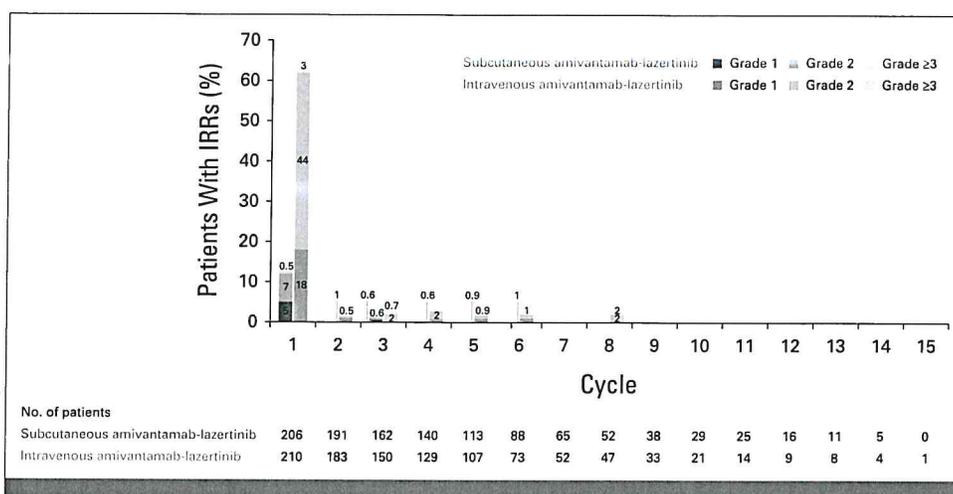


FIG A6. Incidence of IRRs by treatment cycle. IRR was counted only once per time frame per patient, and the event experienced by the patient with the worst toxicity was used. AE, adverse event; IRR, infusion-related reaction.

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.

^aThe objective response (complete or partial response as best response) was assessed using RECIST, v1.1 and analyzed using logistic regression.

^bAmong all responders.

^cNot 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.

^aEvents 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.

^aEvents 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.

^aEvents in this category are listed according to decreasing incidence in the subcutaneous group.

^bGrade 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.

^aEvents in this category are listed according to decreasing incidence in the prophylactic anticoagulation group.

^bGrade 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.

^aListed are AEs that were reported in at least 3% of patients in either group.

^bListed 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 $\geq 15\%$ 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.

^aEvents 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.

^aEvents are listed according to decreasing incidence in the subcutaneous group.

^bAll events deemed related to any study treatment.

^cOne 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	Phramongkutkiao 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 Pesquisa, Instituto Brasileiro de Controle do Câncer
Alexander I. Spira	Virginia Cancer Specialists
Thatthan Suksombooncharoen	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