Author's Accepted Manuscript

Subcutaneous versus Intravenous Amivantamab, both in Combination with Lazertinib, in Refractory EGFR-mutated NSCLC: Primary Results from the Phase 3 PALOMA-3 Study

Natasha B. Leighl, et al

DOI: 10.1200/JCO.24.01001

To appear in: *Journal of Clinical Oncology*
Accepted Date: June 4, 2024

Please cite this article as: Leighl NB, Akamatsu H, Lim SM, Cheng Y, Minchom AR, Marmarelis ME, Sanborn RE, Yang JC, Liu B, John T, Massutí B, Spira AI, Lee S, Wang J, Li J, Liu C, Novello S, Kondo M, Tamiya M, Korbenfeld E, Moskovitz M, Han J, Alexander M, Joshi R, Felip E, Voon PJ, Danchaivijitr P, Hsu P, Cruz FJSM, Wehler T, Greillier L, Teixeira E, Nguyen D, Sabari JK, Qin A, Kowalski D, Şendur MAN, Xie J, Ghosh D, Alhadab A, Haddish-Berhane N, Clemens PL, Lorenzini P, Verheijen RB, Gamil M, Bauml JM, Baig M, Passaro A. Subcutaneous versus Intravenous Amivantamab, both in Combination with Lazertinib, in Refractory EGFR-mutated NSCLC: Primary Results from the Phase 3 PALOMA-3 Study. doi: 10.1200/JCO.24.01001. Epub 2024 June 10.

Subcutaneous versus Intravenous Amivantamab, both in Combination with Lazertinib, in Refractory *EGFR*-mutated NSCLC: Primary Results from the Phase 3 PALOMA-3 Study

Natasha B. Leighl, MD,[1] Hiroaki Akamatsu, MD, PhD,[2] Sun Min Lim, MD, PhD,[3] Ying Cheng, MD,[4] Anna R. Minchom, MD,[5] Melina E. Marmarelis, MD,[6] Rachel E. Sanborn, MD,[7] James Chih-Hsin Yang, MD, PhD,[8] Baogang Liu, MD,[9] Thomas John, MD,[10] Bartomeu Massutí, MD,[11] Alexander I. Spira, MD, PhD,[12] Se-Hoon Lee, MD, PhD,[13] Jialei Wang, MD,[14] Juan Li, MD,[15] Caigang Liu, MD, PhD,[16] Silvia Novello, MD, PhD,[17] Masashi Kondo, MD, PhD,[18] Motohiro Tamiya, MD,[19] Ernesto Korbenfeld, MD,[20] Mor Moskovitz, MD,[21] Ji-Youn Han, MD, PhD,[22] Mariam Alexander, MD, PhD,[23] Rohit Joshi, MD,[24] Enriqueta Felip, MD, PhD,[25] Pei Jye Voon, MD, MMed,[26] Pongwut Danchaivijitr, MD,[27] Ping-Chih Hsu, MD,[28] Felipe José Silva Melo Cruz, MD,[29] Thomas Wehler, MD, PhD,[30] Laurent Greillier, MD, PhD,[31] Encarnação Teixeira, MD,[32] Danny Nguyen, MD,[33] Joshua K. Sabari, MD,[34] Angel Qin, MD,[35] Dariusz Kowalski, MD, PhD,[36] Mehmet Ali Nahit Şendur, MD, PhD,[37] John Xie, PhD,[38] Debopriya Ghosh, PhD,[38] Ali Alhadab, PharmD, PhD,[39] Nahor Haddish-Berhane, PhD,[40] Pamela L. Clemens, PhD,[40] Patricia Lorenzini, MS,[40] Remy B. Verheijen, PhD,[41] Mohamed Gamil, MD,[40] Joshua M. Bauml, MD,[40] Mahadi Baig, MD,[38] Antonio Passaro, MD, PhD[42] for the PALOMA-3 Investigators†

Affiliations

[1]Princess Margaret Cancer Centre, Toronto, Canada

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

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

[4]Jilin Cancer Hospital, Changchun, China

[5]Drug Development Unit, The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, UK

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

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

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

[9]Harbin Medical University Cancer Hospital, Harbin, China

[10]Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia

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

[12]Virginia Cancer Specialists, Fairfax, VA, USA

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

[14]Fudan University Shanghai Cancer Center, Shanghai, China

[15]Sichuan Cancer Hospital, Sichuan, China

[16]Shengjing Hospital of China Medical University, Liao Ning Sheng, China

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

[18]Department of Respiratory Medicine, Fujita Health University School of Medicine, Aichi, Japan

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

[20]British Hospital of Buenos Aires – Central British Hospital, Buenos Aires, Argentina

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

[22]National Cancer Center, Goyang, Republic of Korea

[23]Medical University of South Carolina, Charleston, SC, USA

[24]Cancer Research SA, Adelaide, Australia

[25]Medical Oncology Department, Vall d'Hebron Barcelona Hospital Campus, Vall d'Hebron Institute of Oncology (VHIO), Universitat Autonoma de Barcelona, Barcelona, Spain

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

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

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

[29]Núcleo de Ensino e Pequisa, Instituto Brasileiro de Controle do Câncer, São Paulo, Brazil

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

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

[32]Medical Oncology, Hospital CUF Descobertas, Lisboa, Portugal

[33]City of Hope National Medical Center, Duarte, CA, USA

[34]Perlmutter Cancer Center, New York University Langone Health, New York, NY, USA

[35]University of Michigan Rogel Cancer Center, Ann Arbor, MI, USA

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

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

[38]Janssen Research & Development, Raritan, NJ, USA

[39]Janssen Research & Development, San Diego, CA, USA

[40]Janssen Research & Development, Spring House, PA, USA

[41]Janssen Research & Development, Leiden, The Netherlands

[42]European Institute of Oncology IRCCS, Milano, Italy

[†]A complete list of investigators in the PALOMA-3 trial is provided in the Appendix.

Corresponding author:

Natasha B. Leighl

Princess Margaret Cancer Centre

7-913 700 University Ave, Toronto, ON, Canada

Email: Natasha.Leighl@uhn.ca

Running Header

Subcutaneous Amivantamab + Lazertinib in Refractory *EGFR*+ NSCLC

Prior Presentation

Presented at the American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA.

Support

This study was funded by Janssen Research & Development, LLC.

Conflicts of Interest

Natasha B. Leighl: **grants or contracts (institution):** AstraZeneca, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Guardant Health, Inivata; **honoraria (CME lectures):** BMS, Janssen, Merck; **travel, accommodations, expenses (CME lectures):** AstraZeneca, MSD, Roche, Janssen, Sanofi, Guardant Health; **participation on data safety monitoring board (uncompensated):** Mirati Therapeutics, Daiichi Sankyo**.**

Hiroaki Akamatsu: **consulting or advisory role** in Amgen, Janssen, Sandoz; **honoraria** from AstraZeneca, Daiichi Sankyo, Eli Lilly, Pfizer, MSD, Bristol Myers Squibb Japan, Taiho Pharmaceutical, Chugai Pharma, Boehringer Ingelheim, Ono Pharmaceutical, Amgen, Merck, Nippon Kayaku, Novartis, Takeda; **research funding of institution** from Amgen, Chugai Pharma, MSD.

Sun Min Lim: **consulting or advisory role** in AstraZeneca, Boehringer Ingelheim, Eli Lilly, Takeda, J Ints Bio, BMS, MSD, Yuhan; **research funding of institution** from AstraZeneca, Boehringer Ingelheim, GSK, Roche, BridgeBio Therapeutics, Oscotec, Daiichi Sankyo, Gilead, J Ints Bio; **research funding** from Yuhan, Janssen.

Ying Cheng: Nothing to disclose.

Anna R. Minchom: **consulting or advisory role** in Janssen Oncology, Merck, Takeda, Genmab, Faron Pharmaceuticals; **honoraria** from Bayer, Novartis Pharmaceuticals UK Ltd, Chugai Pharma, Janssen, Merck, GSK, Seagen; **research funding of institution** from Merck, MSD Oncology, Astex Pharmaceuticals; **travel, accommodations, and expenses** from Janssen Oncology.

Melina E. Marmarelis: **stock and other ownership interests** in bluebird bio, Gilead Sciences, Johnson & Johnson, Merck, Pfizer, Portola Pharmaceuticals; **honoraria** from AstraZeneca, Blueprint Medicines, Janssen Oncology, Novocure, Takeda, Targeted Oncology, Thermo Fisher Scientific; **honoraria for institution** from Health Advances; **consulting or advisory role** in AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb/Celgene, Ikena Oncology, Regeneron, Daiichi Sankyo; **research funding of institution** from AstraZeneca, Eli Lilly, Merck, Genentech, Trizell; **travel, accommodations, and expenses** from Boehringer Ingelheim, Novocure.

Rachel E. Sanborn: **advisory board member** at AstraZeneca, EMD Serono, Daiichi Sankyo, Eli Lilly Oncology, Janssen Oncology, Sanofi-Aventis, Regeneron, Mirati Therapeutics, GSK, G1 Therapeutics; **invited speaker** for Illumina; **steering**

committee member at GSK, Janssen Oncology; **research funding** from Merck, AstraZeneca, Jounce; **research funding of institution** from Bristol Myers Squibb.

James Chih-Hsin Yang: **honoraria** from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, MSD, Novartis, Ono Pharmaceutical, Pfizer, Roche, Takeda; **consulting or advisory role** in AbbVie, Amgen, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb/Celgene, Clovis Oncology, Daiichi Sankyo, G1 Therapeutics, Hansoh, Incyte, Eli Lilly, Merck Serono, MSD Oncology, Novartis, Ono Pharmaceutical, Pfizer, Takeda, Yuhan; **consulting fees to institution** from Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, GSK, Janssen, Merck Serono, MSD Oncology, Novartis, Takeda; **travel, accommodations, and expenses** from Pfizer.

Baogang Liu: Nothing to disclose.

Thomas John: **honoraria** from AstraZeneca; **consulting or advisory role** in Bristol Myers Squibb, AstraZeneca, Amgen, Roche, Pfizer, Takeda, Boehringer Ingelheim, MSD, Merck, Puma Biotechnology, Specialised Therapeutics, Gilead Sciences, Seagen, Johnson & Johnson; **research funding** from AstraZeneca.

Bartomeu Massutí: **consulting or advisory role** in Roche, Boehringer Ingelheim, AstraZeneca, Merck Serono, Janssen; **speakers bureau member** at Roche, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Sanofi/Regeneron, Janssen Oncology, Pfizer**; travel, accommodations, and expenses** from Roche, MSD Oncology, AstraZeneca.

Alexander I. Spira: **consulting or advisory role** in Array BioPharma, Incyte, Amgen, Novartis, Mirati Therapeutics, Gritstone bio, Jazz Pharmaceuticals, Merck, Bristol Myers Squibb, Takeda, Janssen Research & Development, Mersana, Blueprint Medicines, Gritstone bio, Daiichi Sankyo/AstraZeneca, Regeneron, Eli Lilly, Black Diamond Therapeutics, Sanofi; **consulting fees to institution** from AstraZeneca/MedImmune; **leadership role** in NEXT Oncology; **stock and ownership interests** in Eli Lilly; **honoraria** from CytomX Therapeutics, AstraZeneca/MedImmune, Merck, Takeda, Amgen, Janssen Oncology, Novartis, Bristol Myers Squibb, Bayer; **research funding of institution** from Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, Incyte, AbbVie, Ignyta, Takeda, MacroGenics, CytomX Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, Loxo Oncology, Arch Therapeutics, Gritstone bio, Plexxikon, Amgen, Daiichi Sankyo, ADC Therapeutics, Janssen Oncology, Mirati Therapeutics, Rubius Therapeutics, Synthekine, Mersana, Blueprint Medicines, Regeneron, Alkermes, Revolution Medicines, Medikine, Black Diamond Therapeutics, BluPrint Oncology, NALO Therapeutics, Scorpion Therapeutics, ArriVent Biopharma, Revolution Medicines.

Se-Hoon Lee: **honoraria** from AstraZeneca/MedImmune, Roche, Merck, Eli Lilly, Amgen; **consulting or advisory role** in AstraZeneca, Roche, Merck, Pfizer, Eli Lilly; **research funding** from Merck.

Jialei Wang: Nothing to disclose.

Juan Li: Nothing to disclose.

Caigang Liu: Nothing to disclose.

Silvia Novello: **consulting or advisory role** in Pfizer; **honoraria** from AstraZeneca, Amgen, Novartis, Sanofi, Thermo Fisher, Roche, Takeda, Janssen, Pfizer, Eli Lilly, BeiGene; **participation on data safety monitoring board or advisory board** at BeiGene, Pfizer, Janssen, AstraZeneca.

Masashi Kondo: **research funding** from Chugai Pharma, Ono Pharmaceutical, MSD K.K, Takeda, Daiichi Sankyo, AstraZeneca; **honoraria** from Chugai Pharma, Eli Lilly, Pfizer, AstraZeneca, Ono Pharmaceutical, Bristol Myers Squibb, MSD K.K, Takeda, Daiichi Sankyo.

Motohiro Tamiya: **honoraria** from Chugai Pharma, Boehringer Ingelheim, AstraZeneca, Pfizer, Eli Lilly, Ono Pharmaceutical, Bristol Myers Squibb, MSD.

Ernesto Korbenfeld: Nothing to disclose.

Mor Moskovitz: **honoraria** from AstraZeneca, Roche, MSD, Bristol Myers Squibb, Janssen, Pfizer, Takeda; **consulting or advisory role** in AstraZeneca, Roche, Merck, Pfizer, MSD, Amgen, Bayer, Novartis; **research funding** from AstraZeneca, Bristol Myers Squibb.

Ji-Youn Han: **grants or contracts** from Pfizer, Takeda, Ono Pharmaceutical; **honoraria** from AstraZeneca, Janssen, Merck, Takeda, Yuhan, Novartis, Pfizer; **payment for expert testimony** from AstraZeneca; **consulting role** in AstraZeneca, Janssen, Amgen, Oncobix, Daiichi Sankyo, Merck, Novartis, Abion, Takeda; **participation on a data safety monitoring board or advisory board** at AstraZeneca, Janssen; **leadership role** in National Cancer Drug Assessment Committee.

Mariam Alexander: **participation on a Data Safety Monitoring Board or Advisory Board** in Amgen, BioAtla.

Rohit Joshi: **advisory role or speakers bureau member** at MSD, AstraZeneca, Bristol Myers Squibb, Roche, Gilead Sciences.

Enriqueta Felip: **advisory role or speakers bureau member** at AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Roche, Genentech, Gilead Sciences, GSK, Janssen, Medical Trends, Medscape, Merck Serono, MSD, Novartis, PeerVoice, Peptomyc, Pfizer, Regeneron, Sanofi, Takeda, Turning Point Therapeutics; **independent board member** at Grifols.

Pei Jye Voon: **consulting or advisory role** in AstraZeneca, Ipsen, MSD, Novartis, Pfizer, BeiGene, Amgen; **research funding** from AstraZeneca, Novartis, Boehringer Ingelheim, Janssen-Cilag, Johnson & Johnson, Viracta Therapeutics Inc, Roche, Merck KGaA, MSD, BeiGene, RMC.

Pongwut Danchaivijitr: **honoraria** from Roche, Bristol Myers Squibb, MSD, Janssen, Astellas Pharma; **consulting or advisory role** in Roche, Bristol Myers Squibb, MSD, Janssen, Astellas Pharma, Eisai; **speakers bureau member** at Roche, Bristol Myers Squibb, MSD, Janssen, Astellas Pharma, Amgen, Eisai; **research funding** from MSD, Roche, Janssen.

Ping-Chih Hsu: Nothing to disclose.

Felipe José Silva Melo Cruz: **honoraria** from MSD, Janssen; **consulting or advisory role** in Bayer; **travel, accommodations, expenses** from Astellas.

Thomas Wehler: **grants or contracts** from Boehringer Ingelheim, AstraZeneca; **consulting fees** from Janssen, Boehringer Ingelheim, AstraZeneca; **honoraria** from Janssen, Boehringer Ingelheim, AstraZeneca; **payment for expert testimony** from

Janssen, Boehringer Ingelheim, AstraZeneca; **travel, accommodations, expenses** from Janssen, Boehringer Ingelheim**;** ; **participation on data safety monitoring board or advisory board** for Janssen, Boehringer Ingelheim, AstraZeneca.

Laurent Greillier: **payment or honoraria** from Bristol Myers Squibb, MSD, Takeda, Pfizer, Roche, Amgen, Sanofi, Janssen, Eli Lilly, Novartis, AstraZeneca; **consulting or advisory role** in Bristol Myers Squibb, MSD, Janssen, Daiichi Sankyo, Sanofi, AstraZeneca, Roche, Amgen, Takeda, Pfizer; **leadership role** as President of the French Lung Cancer Group; **travel, accommodations, and expenses** from Pfizer, MSD, AstraZeneca, Takeda, Amgen.

Encarnacao Teixeira: **invited speaker or advisory board** in AstraZeneca, Eli Lilly, F. Hoffmann La Roche, Pfizer, Boehringer Ingelheim, Bristol Myers Squibb, Merck Serono, MSD, Janssen, Takeda, Novartis, Amgen.

Danny Nguyen: **payment or honoraria** from Janssen; **leadership or fiduciary role** for GRYT Health.

Joshua K. Sabari: **advisory role** in AstraZeneca, Genentech, Janssen, Pfizer, Regeneron, Sanofi Genzyme, Takeda, Mirati Therapeutics.

Angel Qin: **grants or contracts** from LUNGevity, AstraZeneca, Genentech, Merck, Clovis; **honoraria** from OncLive, Medscape, Dava Oncology; **participation on data safety monitoring board or advisory board** for Amgen, Summit Therapeutics, Regeneron, Strata Oncology.

Dariusz Kowalski: **participation in advisory board** for Roche, AstraZeneca, Bristol Myers Squibb, MSD, Pfizer, Takeda, Sanofi-Aventis, Amgen, Johnson & Johnson, Novartis.

Mehmet Ali Nahit Sendur: **consulting role** in Roche, AstraZeneca, Pfizer, Novartis, Astellas Pharma, Bristol Myers Squibb, MSD, Eli Lilly, Gilead Sciences, Takeda; **honoraria** from Roche, AstraZeneca, Pfizer, Novartis, Astellas Pharma, Bristol Myers Squibb, MSD, Eli Lilly, Gilead Sciences, Takeda.

John Xie: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Debropriya Ghosh: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Ali Alhadab: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Nahor Haddish-Berhane: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Pamela L. Clemens: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Patricia Lorenzini: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Remy B. Verheijen: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Mohamed Gamil: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Joshua M. Bauml: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Mahadi Baig: **employee** of Janssen and **may hold stock** in Johnson & Johnson.

Antonio Passaro: **consulting or advisory role** in Roche/Genentech, Bristol Myers Squibb, AstraZeneca, MSD Oncology, Pfizer, Boehringer Ingelheim, Johnson &

Johnson/Janssen, Novartis, Daiichi Sankyo Europe GmbH, Bayer; **speakers bureau member** at AstraZeneca, Johnson & Johnson/Janssen, Boehringer Ingelheim, Daiichi Sankyo Europe GmbH, MSD Oncology.

Data sharing statement

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

Acknowledgments

We wish to 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.

Context Summary

Key objective:

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

Knowledge generated:

Subcutaneous amivantamab-lazertinib demonstrated noninferior pharmacokinetics and objective response rates, with a 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. 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.

Abstract

Purpose: Phase 3 studies of intravenous amivantamab demonstrated efficacy across *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 following osimertinib and platinum-based chemotherapy were randomized 1:1 to receive subcutaneous or intravenous amivantamab, both combined with lazertinib. Co-primary pharmacokinetic noninferiority endpoints were trough concentrations (C_{trough}; on cycle-2-day-1 or cycle-4-day-1) and cycle-2 area under the curve ($AUC_{D1\text{-}D15}$). Key secondary endpoints were objective response rate (ORR) and progression-free survival (PFS). Overall survival (OS) was a predefined exploratory endpoint.

Results: Overall, 418 patients underwent randomization (subcutaneous group, n=206; intravenous group, n=212). Geometric mean ratios of C_{trough} for subcutaneous to intravenous amivantamab were 1.15 (90% CI, 1.04-1.26) at cycle-2-day-1 and 1.42 (90% CI, 1.27-1.61) at cycle-4-day-1; the cycle-2 $AUC_{D1\text{-}D15}$ was 1.03 (90% CI, 0.98-1.09). 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, 0.42-0.92; nominal *P*=0.02). Fewer patients in the subcutaneous group experienced infusion-related reactions (13% versus 66%) and venous thromboembolism (9% versus 14%)

versus the intravenous group. Median administration time for first infusion was reduced to 4.8 minutes (range, 0-18) for subcutaneous amivantamab from 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; 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 infusion-related reactions, increased convenience, and prolonged survival.

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 3 PAPILLON trial) and as a monotherapy following disease progression on platinum-based chemotherapy (phase 1 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 based on the phase 3 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 1-2.[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 1 PALOMA trial, revealing low rates of IRRs and associated symptoms, with an administration time ≤7 minutes for the every-2-week and every-3-week regimens, and up to 10 minutes for the 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 3, 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 following disease progression on osimertinib and platinum-based chemotherapy.

Patients and Methods

Patients

Eligible patients were ≥18 years, 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 online protocol.

Study Design and Treatment

Patients were randomized (1:1) to receive subcutaneous amivantamab-lazertinib or intravenous amivantamab-lazertinib in 28-day cycles (**Appendix Fig. 1**). Subcutaneous amivantamab (concentration, 160 mg/mL), co-formulated with hyaluronidase (rHuPH20), was administered by manual injection at a dose of 1600 mg (2240 mg for ≥80 kg weight) 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 1050 mg (1400 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 daily.

Randomization was stratified by history of brain metastases (yes or no), *EGFR* mutation type (Ex19del versus L858R), race (Asian versus non-Asian), and type of last therapy (osimertinib versus 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 co-primary pharmacokinetic outcomes for noninferiority were trough concentrations (C_{trough}; either pre-dose 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 endpoint. A complete list of outcomes and definitions is available in the protocol.

Disease assessments (CT, MRI, or other imaging) were performed within 28 days before randomization, then at 6 weeks (maximum, 7 weeks) after randomization 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 Response Evaluation Criteria In Solid Tumors (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 (CTCAE), v5.0. Pharmacokinetic and immunogenicity assessments for amivantamab were conducted using validated assays on blood serum and plasma samples collected throughout the trial until 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 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 endpoint. Efficacy analysis included all randomized 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 0.05 allocated to each of the co-primary pharmacokinetic endpoints and 80% power with a one-sided alpha of 0.025 allocated to ORR. For the co-primary endpoints, the power analysis assumes true geometric mean ratios of C_{trough} and $AUC_{D1\text{-}D15}$ to be 1 between the two treatment groups, and a coefficient of variation (CV) of 56% for both endpoints. Additional details can be found in Section 9 of the protocol.

The primary hypotheses were that the lower bounds of the 90% confidence interval (CI) for the geometric mean ratios for subcutaneous versus intravenous amivantamab would be ≥80% (noninferiority margin of 20%) for both co-primary pharmacokinetic endpoints. The noninferiority criterion for the pharmacokinetic primary endpoint is based on the FDA-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% (based on regulatory precedence from other subcutaneous formulations;[17] additional details can be found on the statistical analysis plan, available online). 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 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 co-primary pharmacokinetic endpoints (noninferiority, at a two-sided alpha of 0.05), followed by the key secondary endpoints of ORR (noninferiority) and then PFS (superiority). The key secondary endpoints were tested using a combined two-sided alpha of 0.05.

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 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 randomized (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 prior therapy lines was 2 (range, 1-5 [subcutaneous], 1-4 [intravenous]). Most patients were female, 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 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%) of patients were undergoing treatment in the subcutaneous and intravenous groups, respectively. Time to amivantamab discontinuation is shown in **Appendix Fig. 2**.

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, 1.04-1.26) at cycle-2-day-1 and 1.43 (90% CI, 1.27-1.61) 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, 0.98-1.09). 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 Fig. 3**.

Treatment-emergent anti-amivantamab antibodies were detected in 1 (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, 24-37) in the subcutaneous and 33% (95% CI, 26-39) in the intravenous group (relative risk, 0.92; 95% CI, 0.70-1.23; **Table 2** and **Appendix Fig. 4**). 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 **Fig. 2A.** Median time to response was 1.5 months (range, 1.2-6.9) in the subcutaneous 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-not estimable [NE]) in the subcutaneous and 8.3 months (95% CI, 5.4-NE) in the intravenous group; 29% and 14% of patients, respectively, had a DoR ≥6 months (**Appendix Fig. 5** and **Appendix Table 1**).

The percentage of patients exhibiting stable disease was 45% in the subcutaneous and 38% in the intravenous group. Disease control rate was 75% (95% CI, 69-81) in the subcutaneous and 71% (95% CI, 64-77) in the intravenous group (**Appendix Table 1**). PFS was tested for superiority of subcutaneous versus intravenous amivantamab, with a median PFS of 6.1 months (95% CI, 4.3-8.1) and 4.3 months (95% CI, 4.1-5.7), respectively, but did not reach statistical significance (HR for disease progression or death, 0.84; 95% CI, 0.64-1.10; *P*=0.20; **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, 79-89) and 65% (95% CI, 52-74) in the subcutaneous group, and 75% (95% CI, 68-80) and 51% (95% CI, 37-64) in the intravenous group. Overall survival was significantly longer for the subcutaneous compared to the intravenous group (HR for death, 0.62; 95% CI, 0.42-0.92; nominal *P*=0.02; **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 2**).

The proportion of patients reporting an IRR was 13% in the subcutaneous and 66% in intravenous group (**Fig. 3**), with 1 (0.5%) and 8 (4%) patients experiencing a grade 3 event, respectively (no grade 4 or 5 events were reported). All infusion-related AEs ranged between 0%-6% in the subcutaneous and 2%-20% in the intravenous group. Most IRRs occurred during cycle-1 (**Appendix Fig. 6**). There were no discontinuations due to IRRs in the subcutaneous versus 4 (2%) in the intravenous group.

VTE was reported in 9% of patients in the subcutaneous and 14% in the intravenous group, with pulmonary embolism and deep-vein thrombosis being the most common (**Appendix Table 3**). 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 4**). 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 Table 5** and **Appendix Table 6**). 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 due to 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 and 25% in the intravenous group; corresponding rates due to grade ≥3 AEs were 3% and 4%, respectively. Rash was the leading cause for dose reductions in the subcutaneous and intravenous groups (8% versus 4%) with similar incidence of all-grade rash (46% versus 43%) and grade ≥3 rash (3% versus 4%) between both groups (**Appendix Table 7**). The median duration of rash was 31 days in the subcutaneous and 44 days in the intravenous group. Most common reasons for discontinuation are presented in **Appendix Table 7**. Discontinuation of all agents due to treatment-related AEs was 9% and 12% in the subcutaneous and intravenous groups, respectively. Treatment-related AEs are shown in **Appendix Table 8**.

Death due to AEs occurred in 7 (3%) and 10 (5%) patients in the subcutaneous and intravenous groups, respectively. All grade 5 AEs are listed in **Appendix Table 9**.

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*<0.001; **Fig. 4**). Data at cycle-3-day-1 were consistent with cycle-1-day-1. At 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*<0.001).

Discussion

Subcutaneous amivantamab-lazertinib demonstrated noninferior pharmacokinetics and antitumor activity (objective response) compared to 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 $AUC_{D1\text{-}D15}$) remained similar between groups. Consistent with the established flat exposure-safety relationships previously reported,[18] the higher C_{trough} observed with subcutaneous amivantamab-lazertinib did not negatively impact its safety profile, as AE incidence was comparable between groups.

While ORR was noninferior for the subcutaneous versus 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. While statistical significance for superiority was not achieved, PFS was also numerically longer in the subcutaneous 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*=0.02). The observed benefit in the subcutaneous group was consistent across all efficacy endpoints and may be driven by better tolerability, as indicated by the longer time to treatment discontinuation. Further, 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.[22] Although dose reduction rates were marginally higher in the subcutaneous group, dose reductions due to grade ≥3 AEs were comparable (3% vs 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.

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 (NCT04487080) and MARIPOSA-2 trials (NCT04988295).[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 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 prior 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 (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 amivantamab administered every 3 weeks and every 4 weeks,[9,26] which may further increase convenience for the patient and 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 to the intravenous formulation, subcutaneous amivantamab maintains efficacy, improves patient and healthcare provider experience, and substantially reduces the rate of IRRs.

References

1. Moores 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 76:3942-53, 2016

2. 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

3. 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

4. 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

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. Journal of Clinical Oncology 41:9013-9013, 2023

6. RYBREVANT (amivantamab-vmjw) injection, for intravenous use [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; Revised March 2024

7. Cho BC, Felip E, Spira AI, et al: Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer

(NSCLC): primary results from MARIPOSA, a phase III, global, randomized, controlled trial. Ann Oncol 34:S1306. Abstract LBA14, 2023

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: the 59th Annual Meeting of the American Society of Clinical Oncology (ASCO); June 2-6, 2023; Chicago, IL

10. Leighl N, Cho BC, Hiret 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; September 9-12, 2023; Singapore:Oral presentation OA21.04

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, 2023

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; June 2-6, 2023; Chicago, IL, USA, 2023

15. European Medicines Agency: Concept paper for the development of a guideline on 4 non-inferiority and equivalence comparisons in clinical 5 trials. Available at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-development-guideline-non-inferiority-equivalence-comparisons-clinical-trials_en.pdf. Accessed May 22, 2024

16. U.S. Food and Drug Administration: Non-inferiority clinical trials to establish effectiveness. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials. Accessed May 22, 2024

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. Trevaskis 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, Felip 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; October 20-24, 2023; Madrid, Spain, 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, 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. Leighl 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). Mini oral presentation at: the European Lung Cancer Congress (ELCC); March 20-23, 2024; Prague, Czech Republic

Figures

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram of Patient Disposition

Figure 2. Objective Response Forest Plot, PFS, and OS

The efficacy population included all patients who had undergone randomization.

In Panel A, the shaded area indicates 95% CIs for the relative risk in all patients; the subgroup analyses were not part of the hypothesis testing and results are reported without adjustment for multiplicity. In Panels B and 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, ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Figure 3. Infusion-related Reactions and Infusion-related AEs

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

AE, adverse events; IRR, infusion-related reaction.

Figure 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 end of treatment (EOT). EOT data could have been collected after administration of the last dose.

[a]C1D2 for patients who received IV amivantamab due to split dosing.

C, cycle; D, day; IV, intravenous; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

Appendix Figure 1. 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 co-formulated with recombinant human hyaluronidase.

bAssessed by modified TASQ.

AUC, area under the concentration-time curve; Ctrough, 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, randomization; TASQ, Therapy Administration Satisfaction Questionnaire.

Appendix Figure 2. 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.

Appendix Figure 3. Observed Concentration-time Profiles, Ctrough, and AUCD1-D15 of Amivantamab

To capture the peak concentration of intravenous amivantamab, 2 samples were analyzed soon after the end of infusion (at 10 minutes and 2 hours following intravenous infusion). The upper and lower end of the boxes indicate the 25th and 75th quartiles, the triangles indicate the means, the horizontal lines within the boxes indicate the medians, and the error bars indicate 95% confidence intervals.

AUC, area under the concentration-time curve; AUCD1-D15, AUC between Cycle 2 Day 1 and Day 15; C, Cycle; Ctrough, observed serum concentration of amivantamab at steady state; D, day.

Appendix Figure 4. Best Percentage Change From Baseline in Target Lesions

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.

Appendix Figure 5. DoR

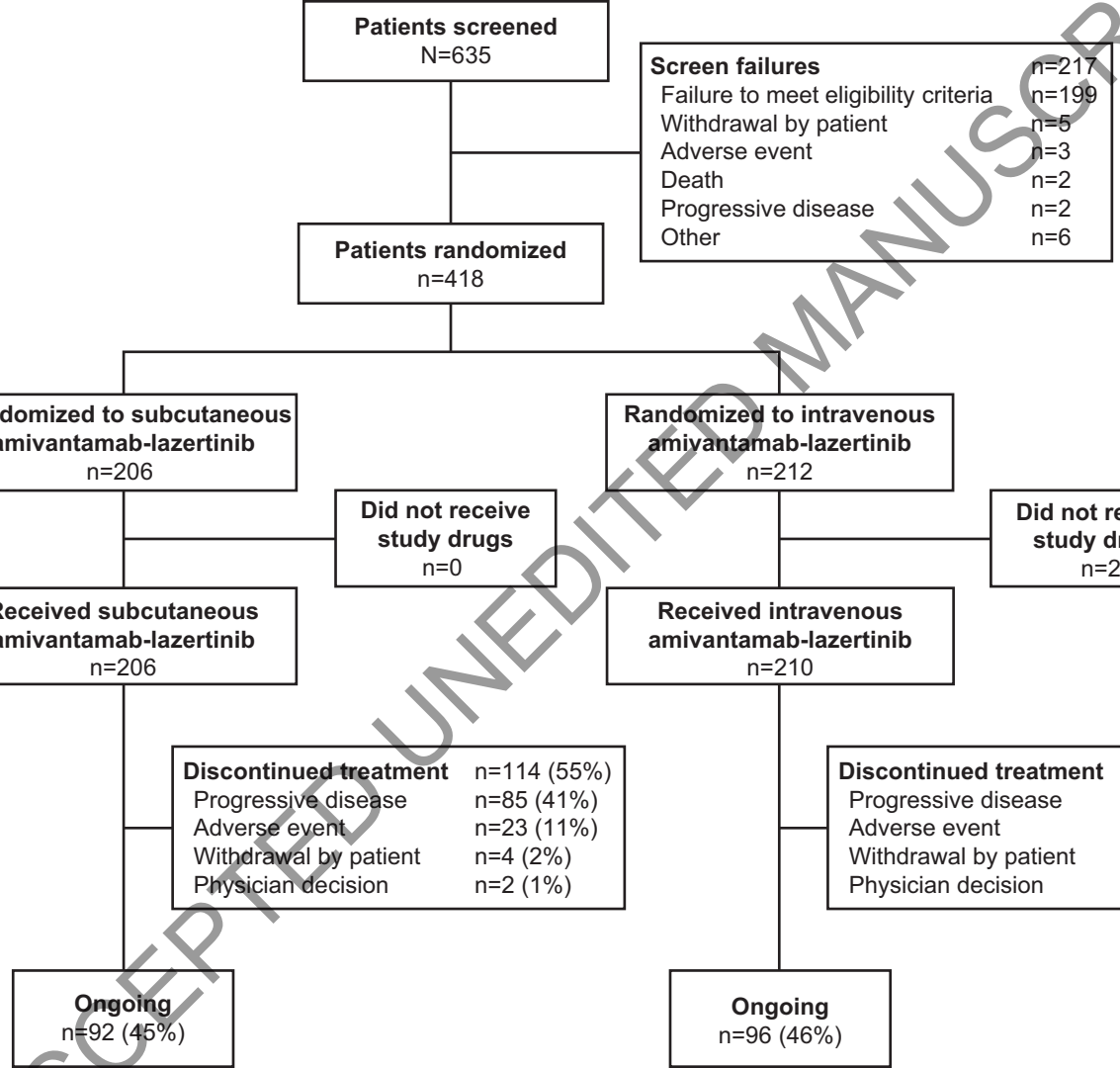
The efficacy population included all patients who had undergone randomization. Included in this analysis were the 55 (confirmed) and 62 (including unconfirmed) responders (out of the 206 patients with measurable disease at baseline by RECIST, v1.1) in the subcutaneous group and the 57 (confirmed) and 69 (including unconfirmed) responders (out of 212 patients) in the intravenous group, respectively. Tick marks indicate censoring of data.

CI, confidence internal; DoR, response duration; NE, not estimable; RECIST, Response Evaluation Criteria In Solid Tumors.

Appendix Figure 6. Incidence of IRRs by Treatment Cycle

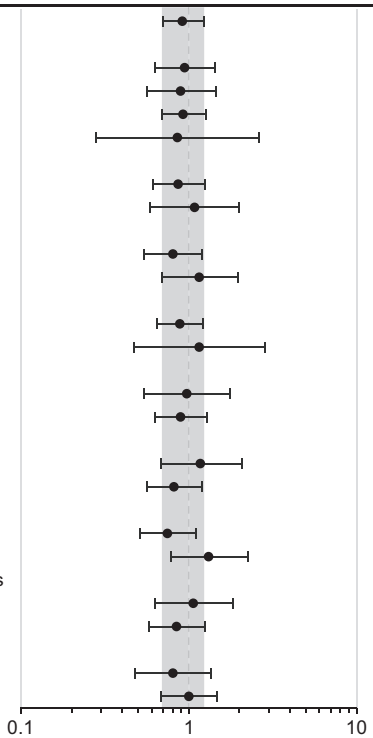
IRR was counted only once per time frame per patient, and the event experienced by the patient with the worst toxicity was used.

AE, adverse event; IRR, infusion-related reaction.

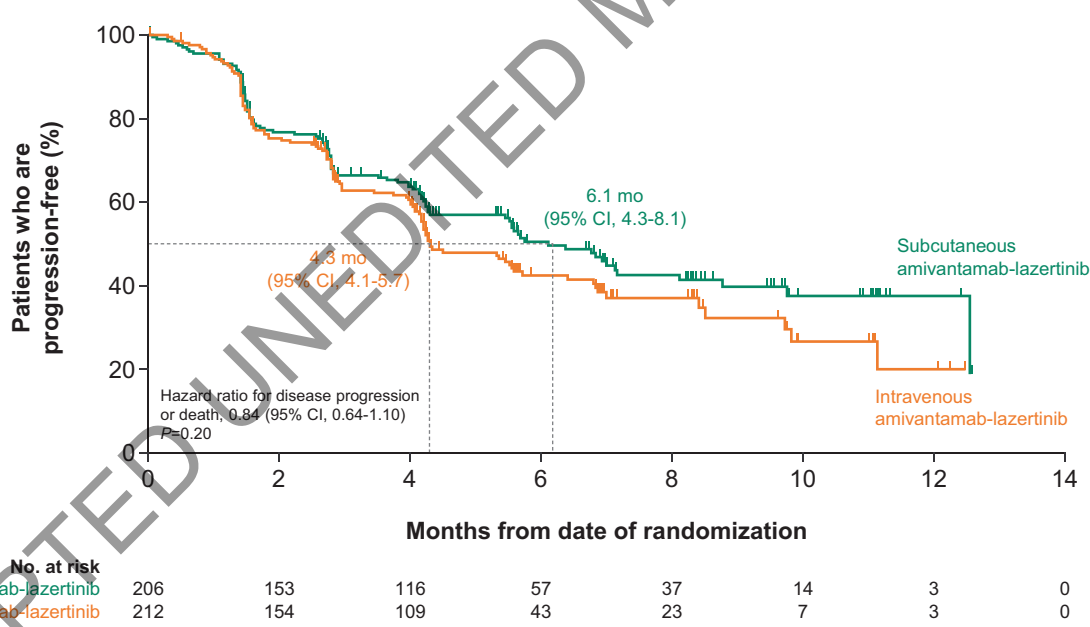


A.

Subgroup	Relative risk (95% CI)	No. of responders/no. of patients (%) Subcutaneous amivantamab-lazertinib	Intravenous amivantamab-lazertinib
All randomized patients	0.92 (0.70-1.23)	62/206 (30)	69/212 (33)
Age category			
<65 years	0.95 (0.63-1.43)	35/133 (26)	38/120 (32)
≥65 years	0.90 (0.56-1.44)	27/73 (37)	31/92 (34)
<75 years	0.93 (0.69-1.26)	57/188 (30)	63/190 (33)
≥75 years	0.86 (0.28-2.61)	5/18 (28)	6/22 (27)
Sex			
Female	0.87 (0.61-1.24)	43/138 (31)	51/141 (36)
Male	1.09 (0.59-1.99)	19/68 (28)	18/71 (25)
Race			
Asian	0.81 (0.54-1.19)	36/126 (29)	46/129 (36)
Non-Asian	1.16 (0.69-1.96)	26/79 (33)	23/81 (28)
Weight category			
<80 kg	0.89 (0.65-1.22)	53/184 (29)	61/184 (33)
≥80 kg	1.16 (0.47-2.86)	9/22 (41)	8/28 (29)
ECOG PS			
0	0.98 (0.54-1.76)	19/58 (33)	20/61 (33)
1	0.90 (0.63-1.29)	43/148 (29)	49/151 (32)
History of smoking			
Yes	1.18 (0.68-2.08)	23/65 (35)	20/67 (30)
No	0.82 (0.56-1.19)	39/141 (28)	49/145 (34)
EGFR mutation			
Ex19del	0.75 (0.51-1.11)	35/135 (26)	48/138 (35)
L858R	1.32 (0.78-2.25)	27/71 (38)	21/74 (28)
History of brain metastases			
Yes	1.07 (0.63-1.83)	24/71 (34)	23/73 (32)
No	0.85 (0.58-1.25)	38/135 (28)	46/139 (33)
Last therapy			
Osimertinib	0.81 (0.48-1.36)	22/91 (24)	28/96 (29)
Chemotherapy	1.00 (0.68-1.45)	40/115 (35)	41/116 (35)

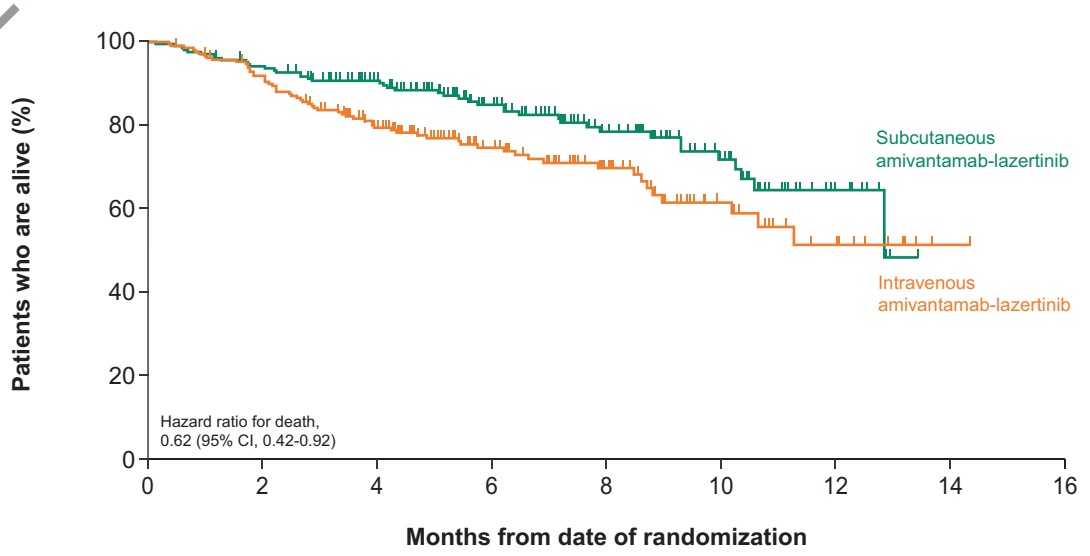


B.

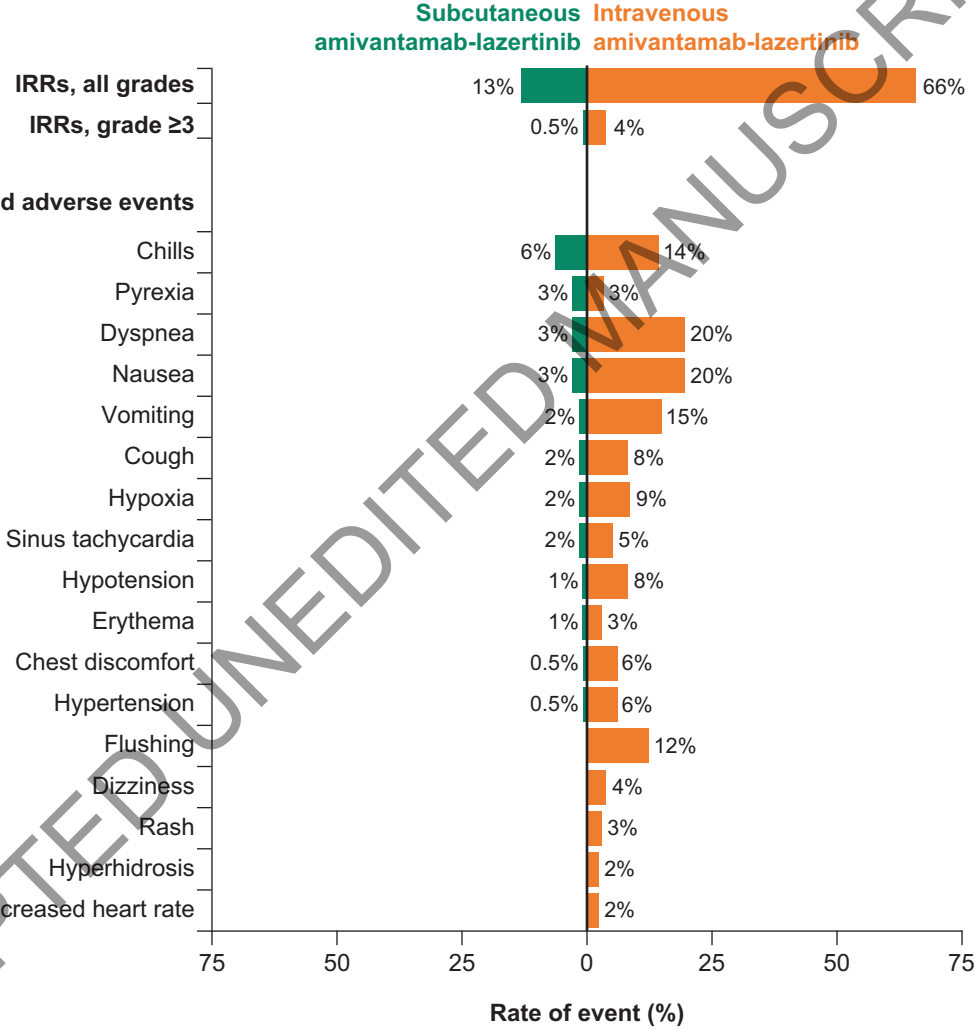


No. at risk								
Subcutaneous amivantamab-lazertinib	206	153	116	57	37	14	3	0
Intravenous amivantamab-lazertinib	212	154	109	43	23	7	3	0

C.



No. at risk									
Subcutaneous amivantamab-lazertinib	206	192	163	109	71	36	10	0	0
Intravenous amivantamab-lazertinib	212	191	144	92	51	24	10	1	0



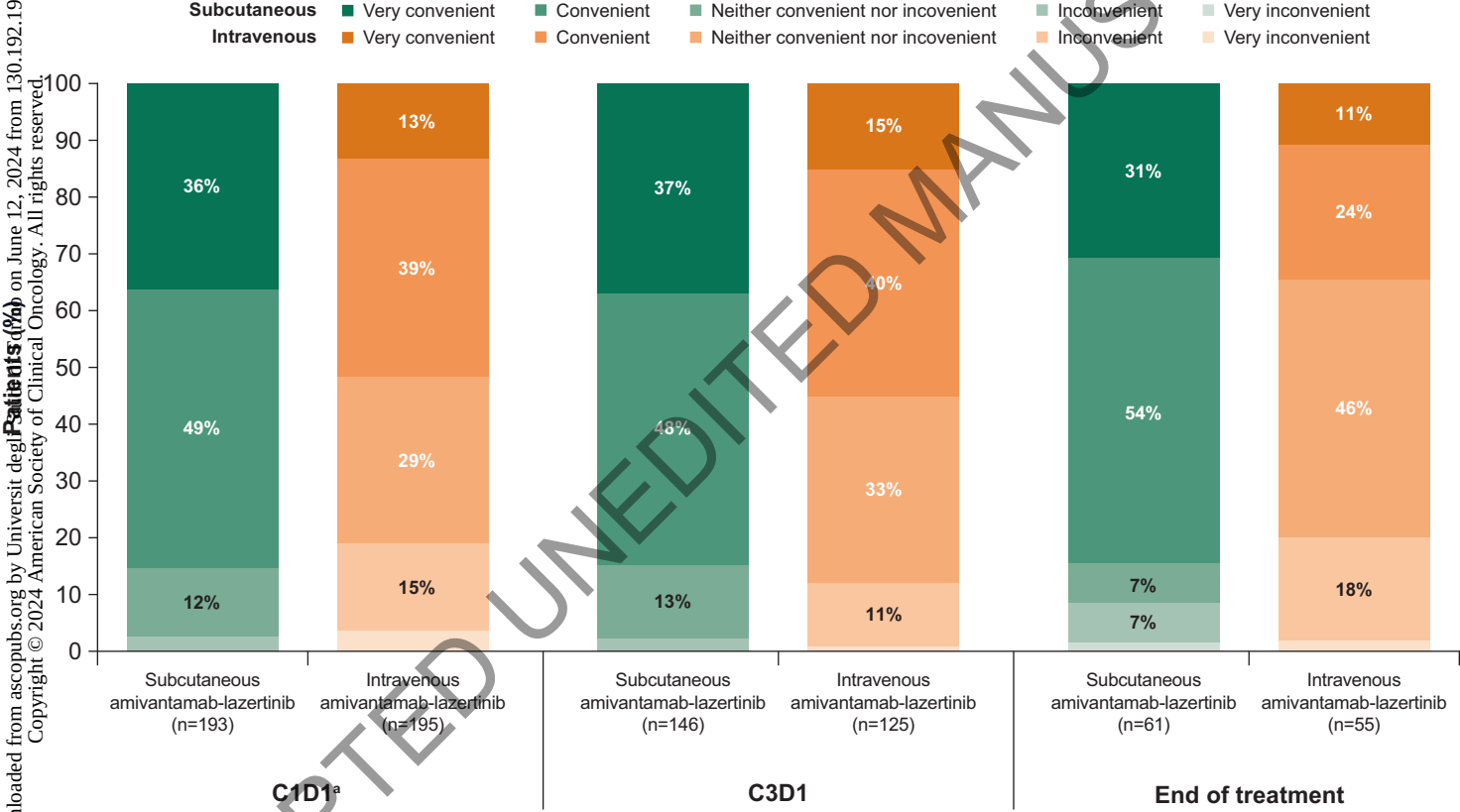


Table 1. Demographic and Clinical Characteristics of Patients at Baseline

Characteristic	Subcutaneous group (n=206)	Intravenous group (n=212)
Age		
Median (range) — years	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 (range) — kg	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. (%)*		
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 (range) — mo	34.5 (2.8-191.3)	33.7 (6.1-156.9)
Median time from metastatic diagnosis (range) — mo	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 randomization — no. (%)		
Exon 19 deletion	135 (66)	138 (65)

L858R	71 (34)	74 (35)
History of brain metastasis		
Yes	70 (34)	72 (34)
No	136 (66)	140 (66)
Last therapy before randomization		
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.

*Russia was counted as part of Europe; Turkey and Israel were counted as part of Asia.

Table 2. Co-primary Pharmacokinetic and Key Efficacy Endpoints

	Subcutaneous group (n=206)	Intravenous group (n=212)	Treatment effect (95% CI)	P Value
Co-primary pharmacokinetic endpoints*				
C_{trough} — µg/mL (%CV)			Geometric mean ratio (90% CI)	
Cycle-2-day-1	365 (33)	314 (32)	1.15 (1.04-1.26)	
Cycle-4-day-1 (steady state)	224 (39)	162 (42)	1.43 (1.27-1.61)	
AUC_{D1-D15} — µg•h/mL (%CV)			Geometric mean ratio (90% CI)	
Cycle 2	142,236 (31)	135,552 (24)	1.03 (0.98-1.09)	
Secondary endpoints				
Objective response†				

Patients (95% CI) — %	30 (24-37)	33 (26-39)	Relative risk for noninferiority, 0.92 (0.70-1.23)‡	0.001
Progression-free survival				
Median (95% CI) — mo	6.1 (4.3-8.1)	4.3 (4.1-5.7)	HR, 0.84 (0.64-1.10)	0.20
Patients (95% CI) — %				
At 6 months	50 (43-58)	42 (35-50)		
At 12 months	37 (28-46)	20 (8-35)		
Overall survival				
Median (95% CI) — mo	12.9 (12.9-NE)	NE (10.2-NE)	HR, 0.62 (0.42-0.92)§	0.02§
Patients (95% CI) — %				
At 6 months	85 (79-89)	75 (68-80)		
At 12 months	65 (52-74)	51 (37-64)		

Abbreviations: %CV, % coefficient of variation; $AUC_{D1\text{-}D15}$, 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.

*The pharmacokinetic population for evaluating the co-primary pharmacokinetic endpoints included all patients who received all doses without dose modifications prior to the respective endpoint and who provided the pharmacokinetic samples necessary to derive each parameter. The efficacy population included all the patients who had undergone randomization.

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

‡Odds ratio (95% CI), 0.87 (0.58-1.32); *P*=0.52. *P* value is calculated via a logistic regression model stratified by brain metastases at baseline (yes vs no), *EGFR* mutation (L858R vs Ex19del), race (Asian vs non-Asian), and last therapy (osimertinib [or another 3rd generation EGFR-TKI] vs chemotherapy).

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

Table 3. Overview of AEs

AE — no. (%)*	Subcutaneous group (n=206)		Intravenous group (n=210)	
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†	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‡	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)
Infusion-related reaction	27 (13)	1 (0.5)	138 (66)	8 (4)

Abbreviations: AE, adverse event.

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

†Excluding infusion/administration-related reactions.

‡Events in this category are listed according to decreasing incidence in the subcutaneous group.

Appendix

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

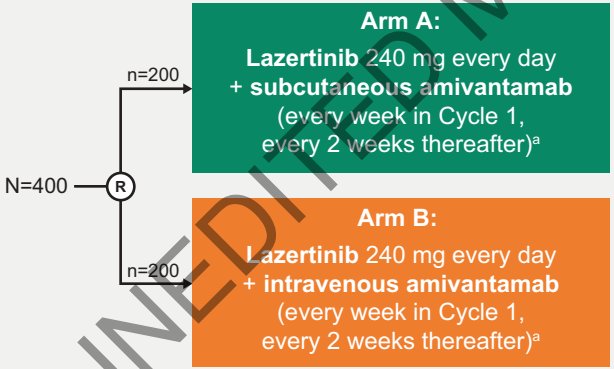
Melina E. Marmarelis	Perelman School of Medicine, University of Pennsylvania
Bartomeu Massutí	Alicante University Dr. Balmis Hospital
Anna R. Minchom	The Royal Marsden Hospital and The Institute of Cancer Research
Sara Moore	The Ottawa Hospital Cancer Centre
Mor Moskovitz	Davidoff Cancer Center, Rabin 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
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

Key eligibility criteria

- Advanced or metastatic *EGFR*-mutated L858R or ex19del NSCLC
- ≥1 measurable lesion
- Progressed on or after osimertinib and platinum-based chemotherapy
- Locally treated brain metastases must be clinically stable and asymptomatic
- ECOG PS 0-1

Stratification: brain metastases, *EGFR* mutation type, race

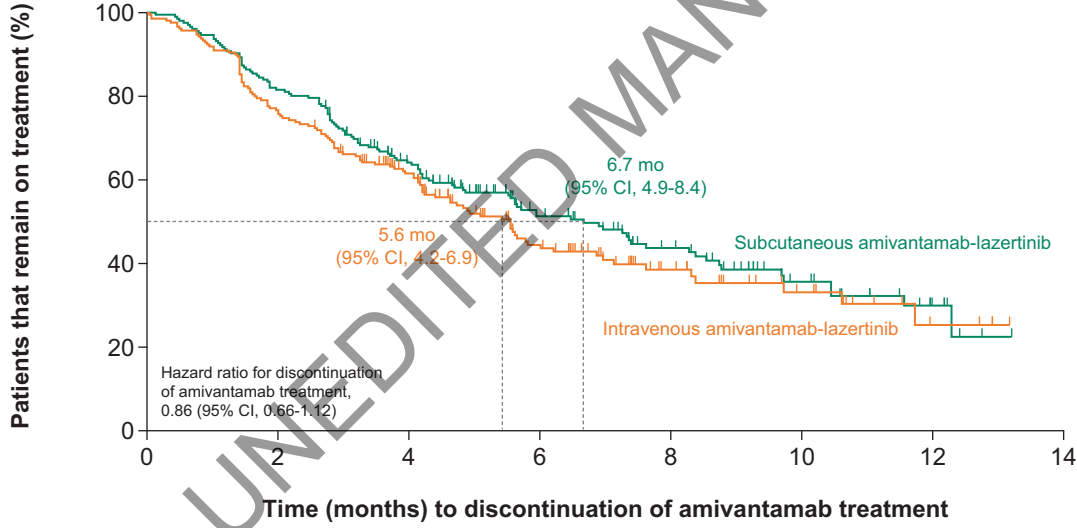


Primary endpoints

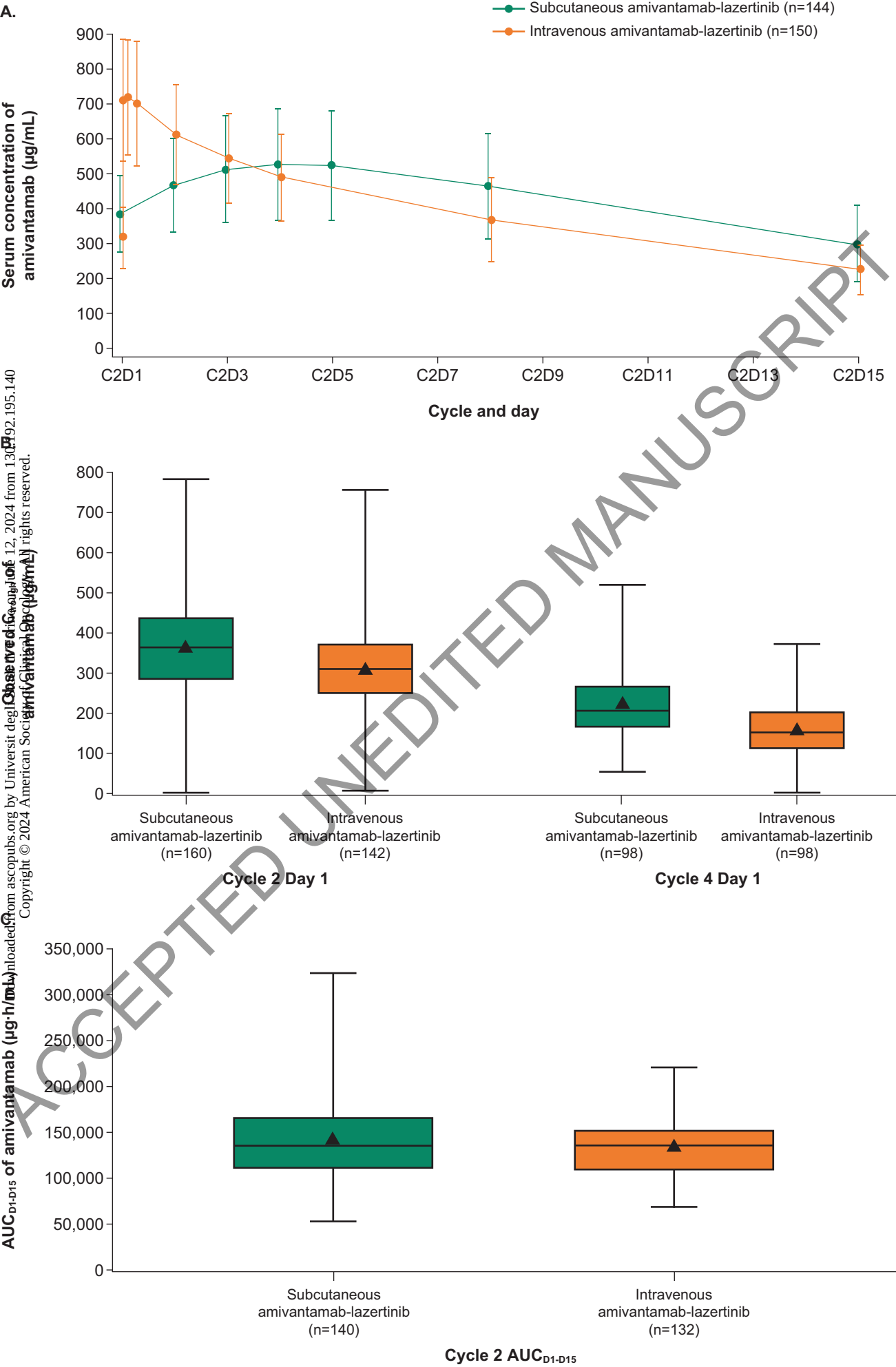
- C_{trough}
  - Cycle 2 Day 1
  - Cycle 4 Day 1
- AUC time curve
  - Cycle 2 Days 1-15

Secondary endpoints

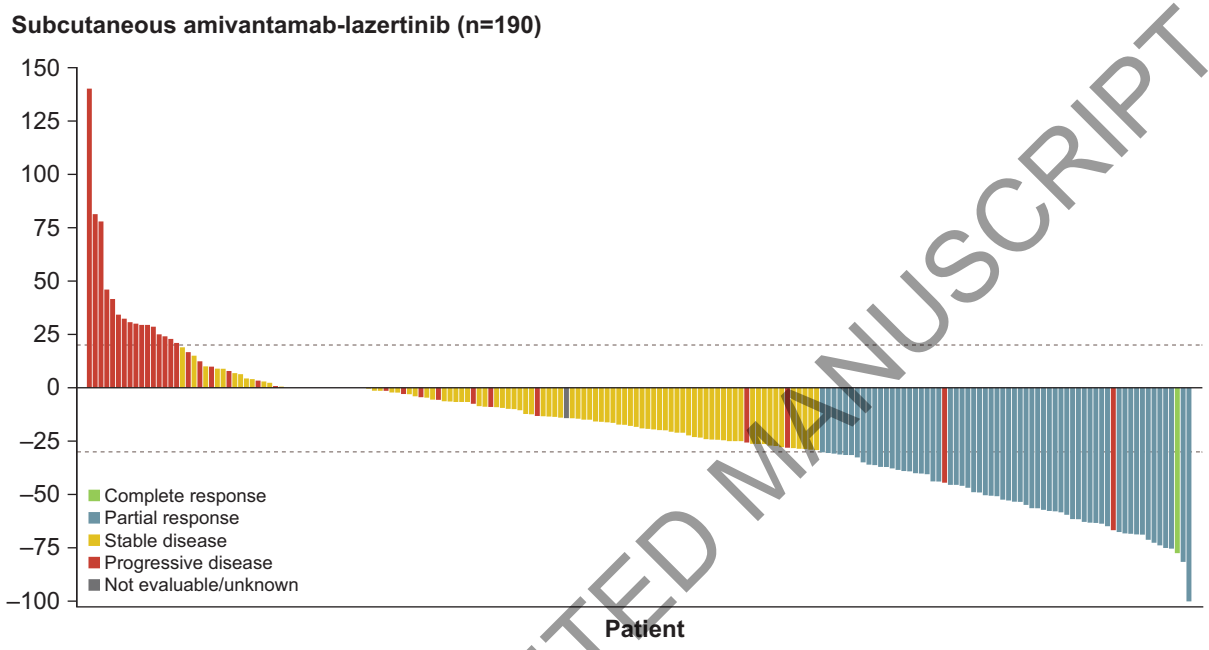
- Objective response rate
- Progression-free survival
- Duration of response
- Time to response
- Patient satisfaction[b]
- Incidence and severity of adverse events, including infusion-related reactions



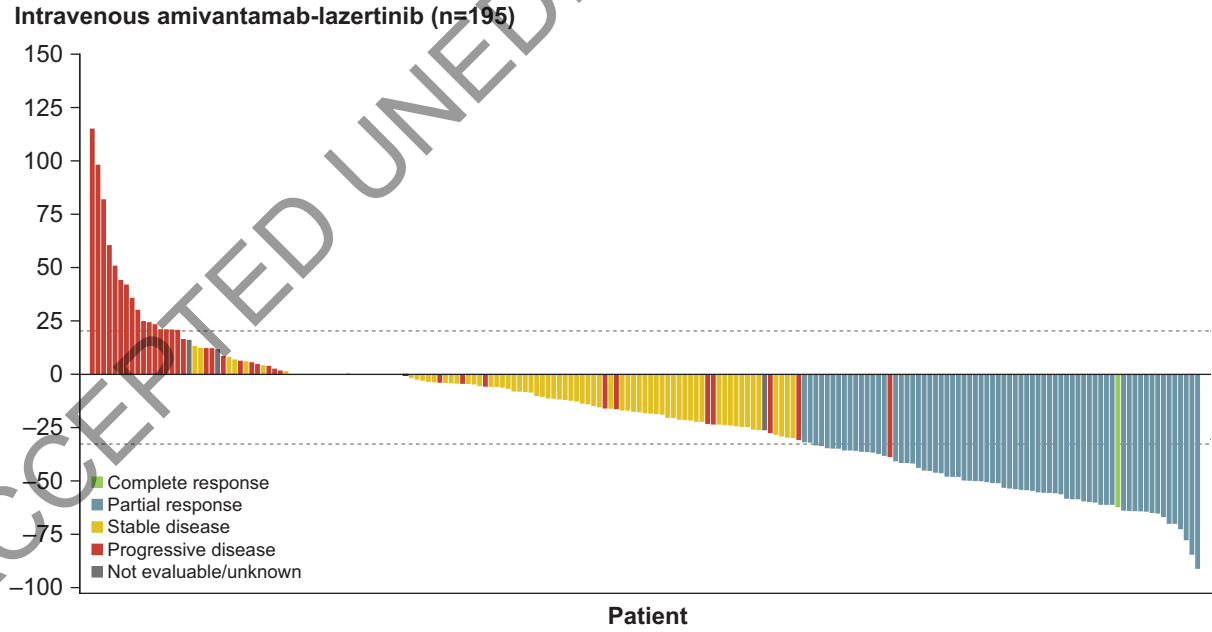
No. at risk								
Subcutaneous amivantamab-lazertinib	206	168	119	69	45	23	7	0
Intravenous amivantamab-lazertinib	210	161	112	57	27	14	4	0



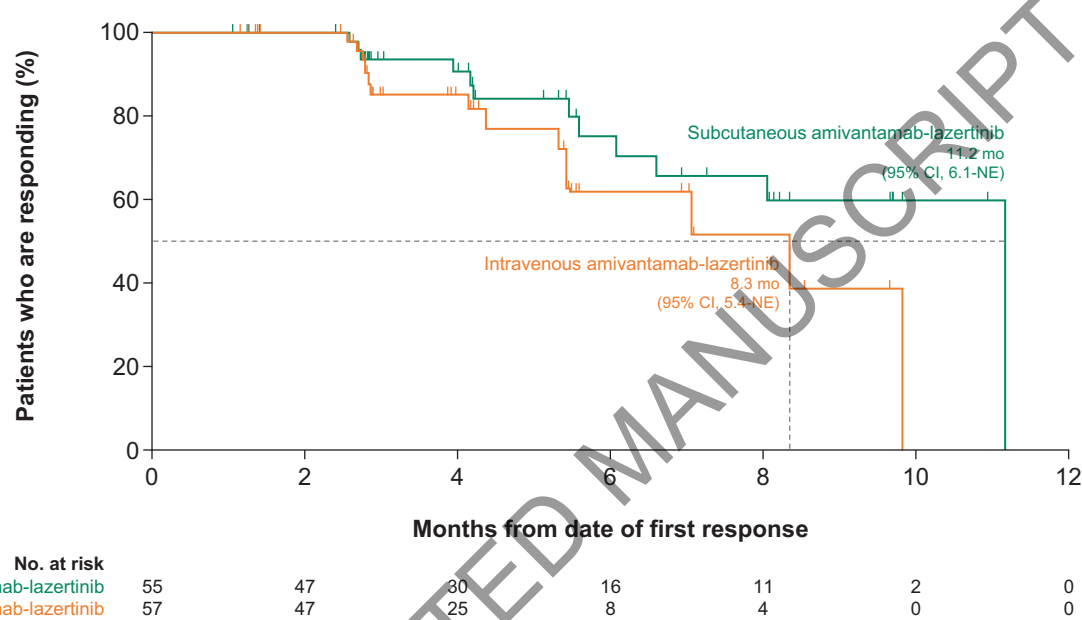
A.



B

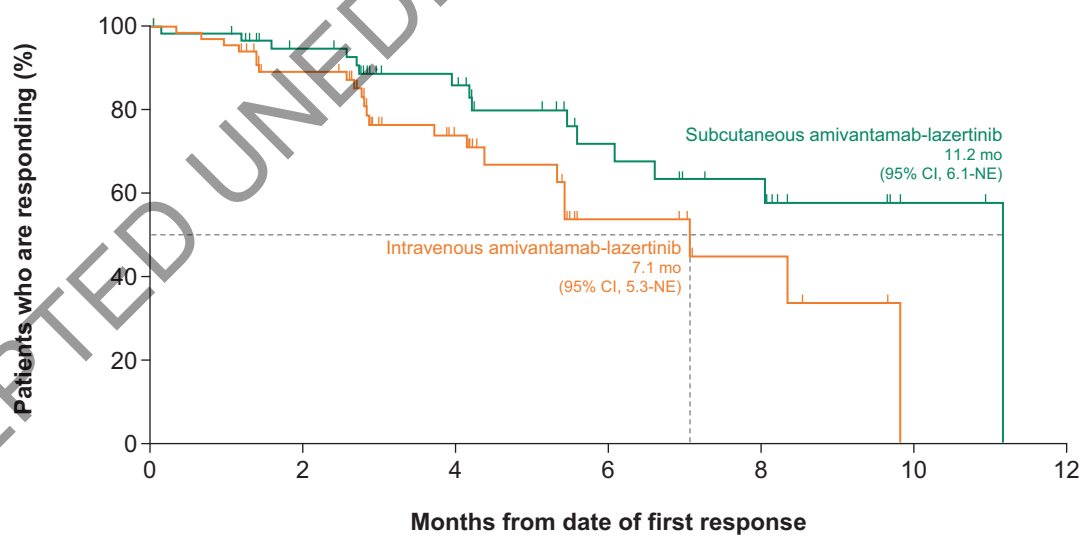


A.

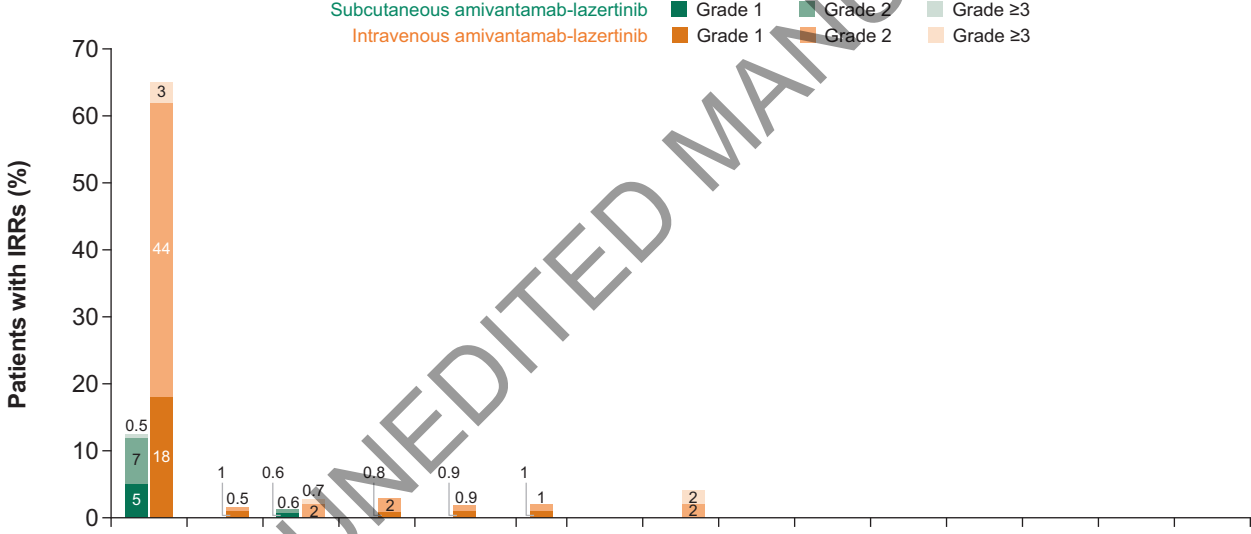


No. at risk							
Subcutaneous amivantamab-lazertinib	55	47	30	16	11	2	0
Intravenous amivantamab-lazertinib	57	47	25	8	4	0	0

B.



No. at risk							
Subcutaneous amivantamab-lazertinib	62	48	31	17	11	2	0
Intravenous amivantamab-lazertinib	69	49	26	8	4	0	0



No. of patients															
Subcutaneous amivantamab-lazertinib	206	191	162	140	113	88	65	52	38	29	25	16	11	5	0
Intravenous amivantamab-lazertinib	210	183	150	129	107	73	52	47	33	21	14	9	8	4	1

Appendix Tables

- **Appendix Table 1.** Response Endpoints
- **Appendix Table 2.** Treatment-emergent Serious AEs Occurring in at Least Two Patients
- **Appendix Table 3.** Venous Thromboembolic Events
- **Appendix Table 4.** Concomitant Anticoagulants
- **Appendix Table 5.** Venous Thromboembolism and Bleeding Events by Anticoagulation Use and by Treatment Group
- **Appendix Table 6.** Venous Thromboembolism and Bleeding Events by Anticoagulation Use Across All Study Patients
- **Appendix Table 7.** AEs Leading to Treatment Interruptions, Reductions, and Discontinuations
- **Appendix Table 8.** Treatment-related AEs
- **Appendix Table 9.** All Grade 5 AEs

Appendix Table 1. Response Endpoints*

	Subcutaneous group (n=206)	Intravenous group (n=212)
Objective response†		
Patients (95% CI) including all responders — %	30 (24-37)	33 (26-39)
Patients (95% CI) including only confirmed responders — %	27 (21-33)	27 (21-33)
Best overall response — no. (%)†		
Complete response‡	1 (0.5)	1 (0.5)
Partial response‡	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)§	75 (69-81)	71 (64-77)
DoR		
Median (95% CI) among all responders — mo	11.2 (6.1-NE)	7.1 (5.3-NE)

Median (95% CI) among confirmed responders — mo	11.2 (6.1-NE)	8.3 (5.4-NE)
Time to response		
Median (range) — mo	1.5 (1.2-6.9)	1.5 (1.2-9.9)

Abbreviations: DoR, response duration; NE, not estimable; RECIST, Response Evaluation Criteria In Solid Tumors.

*The efficacy population included all the patients who had undergone randomization.

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

‡Among all responders.

§Not protocol-specified; calculated as the sum of complete response, partial response, and stable disease; all responders were included.

Appendix Table 2. Treatment-emergent Serious AEs Occurring in at Least Two Patients*

Event — no. (%)†	Subcutaneous group (n=206)	Intravenous group (n=210)
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)

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

†Events in this category are listed according to decreasing incidence in the subcutaneous group.

Appendix Table 3. Venous Thromboembolic Events*

Event — no. (%)	Subcutaneous group (n=206)	Intravenous group (n=210)
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†		
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)

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

†Events in this category are listed according to decreasing incidence in the subcutaneous group.

Appendix Table 4. Concomitant Anticoagulants

Anticoagulant use — no. (%)	Subcutaneous group (n=206)	Intravenous group (n=210)
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)

Appendix Table 5. Venous Thromboembolic and Bleeding Events by Anticoagulation Use and by Treatment Group*

	Subcutaneous group (n=206)		Intravenous group (n=210)	
Event — 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 3-4	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†				
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 3-4‡	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

*The safety population included all patients who had undergone randomization and received at least one dose of any trial treatment. The group with any prophylactic anticoagulation included patients who had anticoagulation prior to 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.

†Events in this category are listed according to decreasing incidence in the subcutaneous group.

‡Grade 3-4 events include contusion, gingival bleeding, hemoptysis, hematemesis, and nail bed bleeding.

Appendix Table 6. Venous Thromboembolic and Bleeding Events by Anticoagulation Use Across All Study Patients*

Event — no. (%)	**Any prophylactic anticoagulation (n=335)**	**No prophylactic anticoagulation (n=81)**
Any venous thromboembolic event	32 (10)	17 (21)
Grade 1	5 (1)	3 (4)
Grade 2	23 (7)	9 (11)
Grade 3-4	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†		
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 3-4‡	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

*The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment. The group with any prophylactic anticoagulation included patients who had anticoagulation prior 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. The group with no prophylactic anticoagulation included patients who never took prophylactic anticoagulation during first 4 months of amivantamab and lazertinib combination treatment.

†Events in this category are listed according to decreasing incidence in the prophylactic anticoagulation group.

‡Grade 3-4 events include contusion, gingival bleeding, hemoptysis, hematemesis, and nail bed bleeding.

Appendix Table 7. AEs Leading to Treatment Interruptions, Reductions, and Discontinuations*

Event — no. (%)	Subcutaneous group (n=206)	Intravenous group (n=210)
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†		
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‡		
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‡		
Pneumonitis	7 (3)	6 (3)
Dermatitis acneiform	4 (2)	1 (0.5)
Infusion-related reaction	0	4 (2)

Abbreviation: AE, adverse event.

*The safety population included all patients who had undergone randomization and received at least one dose of any trial treatment. Events are listed according to decreasing incidence in the subcutaneous group.

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

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

Appendix Table 8. Treatment-related AEs*

Event — no. (%)	Subcutaneous group (n=206)		Intravenous group (n=210)	
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†	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)
Diarrhea	36 (17)	3 (1)	31 (15)	2 (1)
Decreased appetite	37 (18)	1 (0.5)	44 (21)	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)

Abbreviation: AE, adverse event.

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

†Events in this category are listed according to decreasing incidence in the subcutaneous group.

Appendix Table 9. All Grade 5 AEs*

Event — no. (%)†	Subcutaneous group (n=206)	Intravenous group (n=210)
Pneumonitis	1 (0.5)‡	3 (1)‡
Respiratory failure	1 (0.5)‡	1 (0.5)
Sudden death	1 (0.5)‡	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)§
Acute myocardial infarction	0	1 (0.5)

Abbreviation: AE, adverse event.

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

†Events are listed according to decreasing incidence in the subcutaneous group.

‡All events deemed related to any study treatment.

§One event deemed related to any study treatment.