Subcutaneous amivantamab vs intravenous amivantamab, both in combination with lazertinib, in refractory *EGFR*-mutated, advanced non-small cell lung cancer

Primary results, including overall survival, from the global, phase 3, randomized controlled PALOMA-3 trial

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Presented by NB Leighl at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Declaration of Interests – Natasha B Leighl

- **Grants or contracts:** Amgen, AstraZeneca, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Roche, Takeda, Guardant Health, Inivata
- **Honoraria:** BeiGene, BMS, Janssen, Merck, Novartis, Takeda
- **Travel, accommodations, expenses:** AstraZeneca, MSD, Roche, Janssen, Sanofi, Guardant Health
- **Participation on Data Safety Monitoring Board or Advisory Board [uncompensated]:** Mirati Therapeutics, Daiichi Sankyo

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Background

- Amivantamab, an EGFR-MET bispecific antibody with immune cell–directing activity,[1-3] is approved as an IV formulation[4]
- IV amivantamab has a first administration time of ≥4 hours and an infusion-related reaction (IRR) rate of 67%[4,5]
- A patient-centric SC program was developed, aiming to reduce administration time
  - The PALOMA study (ClinicalTrials.gov Identifier: NCT04606381) established a recommended phase 2 dose for a Q2W, Q3W, and Q4W schedule and observed a low IRR rate[6]
  - The efficacy and safety of the SC formulation is being evaluated in the PALOMA-2 (NCT05498428)[7] and PALOMA-3 studies for registrational intent in current and future amivantamab indications

SC formulation could enhance patient and provider treatment experience with amivantamab

The global, phase 3, randomized controlled PALOMA-3 trial compares pharmacokinetic, efficacy and safety outcomes to the IV formulation in combination with lazertinib

EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; IV, intravenous; MET, mesenchymal epithelial transition factor receptor; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous.

1. Moores SL, et al. *Cancer Res.* 2016;76(13):3942-3953. 2. Vijayaraghavan S, et al. *Mol Cancer Ther.* 2020;19(10):2044-2056. 3. Yun J, et al. *Cancer Discov.* 2020;10(8):1194-1209. 4. RYBREVANT® (amivantamab-vmjw). Published March 2024. Accessed March 21, 2024. https://www.rybrevant.com. 5. Park K, et al. *Lung Cancer.* 2023;178:166-171. 6. Minchom AR, et al. *J Clin Oncol.* 2023;41(16_suppl):9126. 7. Lim SM, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA. LBA8612.

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PALOMA-3: Phase 3 Study Design

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Disease had progressed on or after osimertinib and platinum-based chemotherapy, irrespective of order
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0–1

Stratification factors

- Brain metastases (yes or no)
- *EGFR* mutation type (Ex19del vs L858R)
- Race (Asian vs non-Asian)
- Type of last therapy (osimertinib vs chemotherapy)

1:1 randomization (N=418)

SC Amivantamab + Lazertinib (n=206)

IV Amivantamab + Lazertinib (n=212)

Dosing (in 28-day cycles)

SC Amivantamab[a,b] (co-formulated with rHuPH20 and administered by manual injection): 1600 mg (2240 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks thereafter

IV Amivantamab[b]: 1050 mg weekly (1400 mg if ≥80 kg) for the first 4 weeks, then every 2 weeks thereafter

Lazertinib: 240 mg PO daily

Prophylactic anticoagulation recommended for the first 4 months of treatment

Co-primary endpoints[c]**:**

- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

Secondary endpoints:

- ORR (noninferiority)
- PFS (superiority)
- DoR
- Patient satisfaction[f]
- Safety

Exploratory endpoints:

- OS

PALOMA-3 (ClinicalTrials.gov Identifier: NCT05388669) enrollment period: August 2022 to October 2023; data cutoff: 03-Jan-2024.

[a]SC amivantamab was co-formulated with rHuPH20 at a concentration of 160 mg/mL. [b]C1 for IV: Days 1 to 2 (Day 2 applies to IV split dose only [350 mg on Day 1 and the remainder on Day 2]), 8, 15, and 22; C1 for SC: Days 1, 8 , 15, and 22; after C1 for all: Days 1 and 15 (28-day cycles). [c]For calculating primary and key secondary outcomes, we estimated that a sample size of 400 patients would provide >95% power for a 1-sided alpha of 0.05 allocated to each of the co-primary endpoints and 80% power with a 1-sided alpha of 0.025 allocated to ORR. A hierarchical testing approach at a 2-sided alpha of 0.05 was used for the co-primary endpoints (noninferiority), followed by ORR (noninferiority) and PFS (superiority), with a combined 2-sided alpha of 0.05. [d]Two definitions of the same endpoint were used as per regional health authority guidance. [e]Measured between C2D1 and C2D15. [f]Assessed by modified TASQ.

AUC, area under the concentration-time curve; C, Cycle; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; rHuPH20, hyaluronidase; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

Baseline Demographics

Demographics and baseline disease characteristics were well balanced between treatment groups

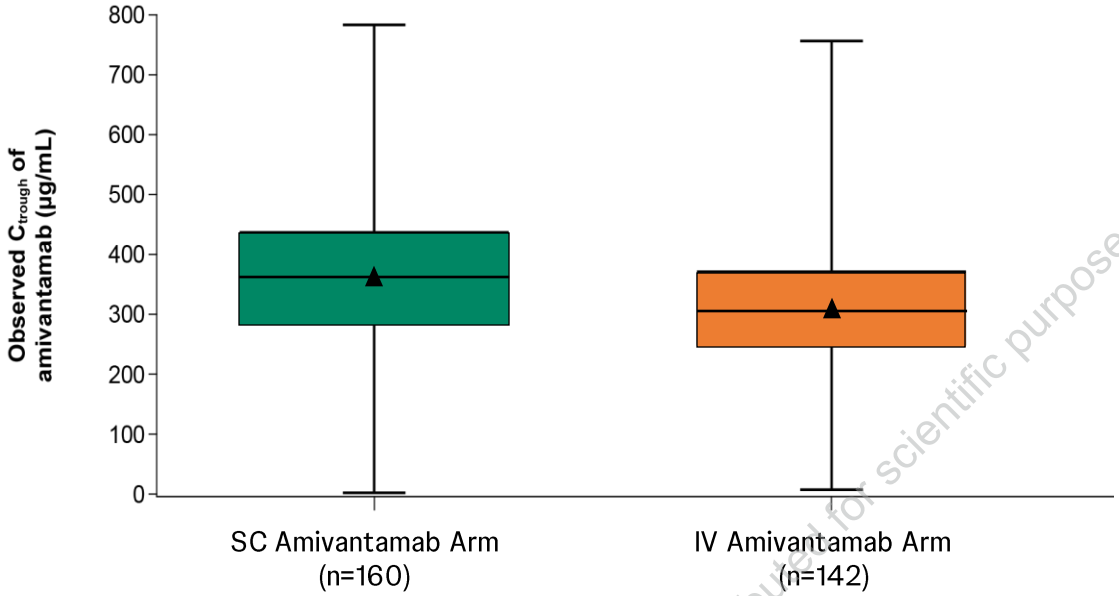
Characteristic, n (%)	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
Median age, years (range)	61 (35–82)	62 (29–81)
Male/female	68 (33) / 138 (67)	71 (33) / 141 (67)
Body weight: <80 kg/≥80 kg	184 (89) / 22 (11)	184 (87) / 28 (13)
Race		
Asian	126 (61)	129 (61)
White	78 (38)	77 (36)
Other[a]	2 (1)	6 (3)
Median prior lines of therapy (range)	**2 (1–5)**	**2 (1–4)**
ECOG PS		
0	58 (28)	61 (29)
1	148 (72)	151 (71)
EGFR mutation type at randomization		
Ex19del	135 (66)	138 (65)
L858R	71 (34)	74 (35)
History of brain metastases	**70 (34)**	**72 (34)**
History of smoking	65 (32)	67 (32)
Last therapy before randomization		
Osimertinib	91 (44)	96 (45)
Chemotherapy	115 (56)	116 (55)
Adenocarcinoma histology	204 (99)	207 (98)

Note: Percentages may not sum to 100 due to rounding. [a]Other includes Black or African American, multiple, and unknown.
ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IV, intravenous; SC, subcutaneous.

Co-primary PK Endpoints Met Noninferiority Criteria

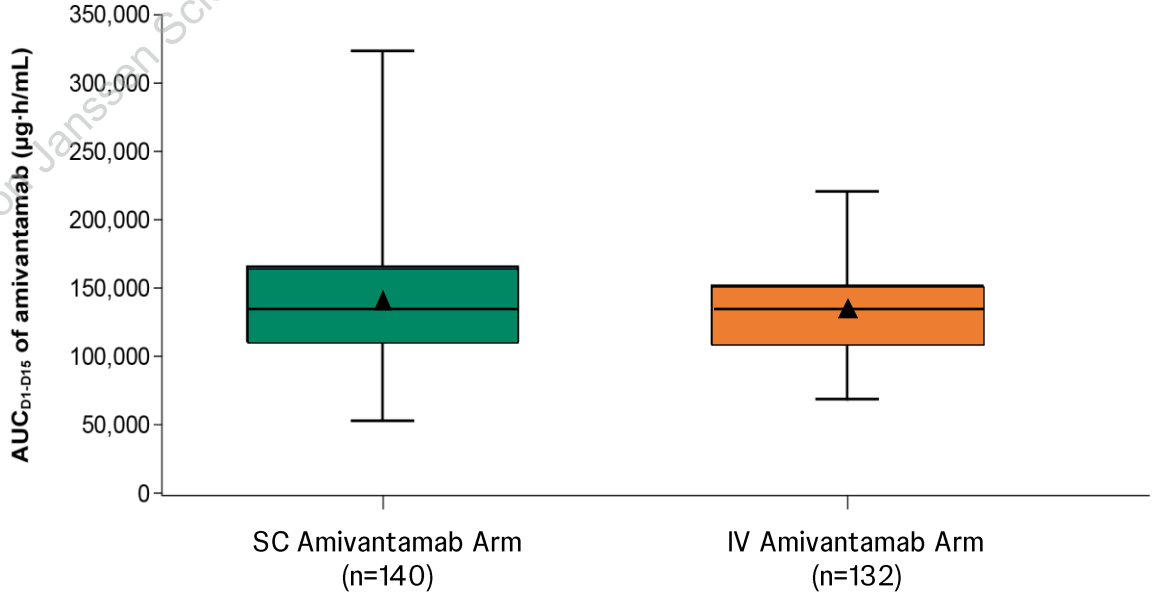
C_{trough} at C2D1

Geometric mean ratio=**1.15**
(90% CI, 1.04–1.26)



C2 $AUC_{D1\text{-}D15}$

Geometric mean ratio=**1.03**
(90% CI, 0.98–1.09)



- Geometric mean ratio for C_{trough} at steady state (C4D1) was 1.43 (90% CI, 1.27–1.61)

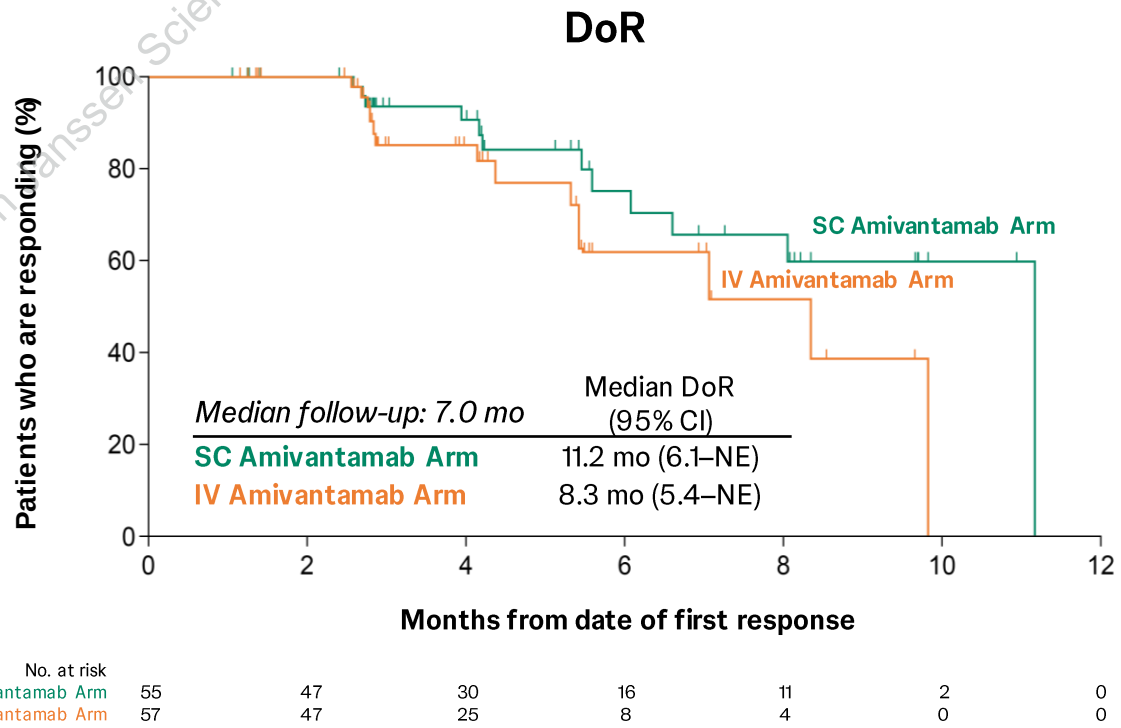
Note: The pharmacokinetic analysis for primary endpoints included all patients who received all doses without dose modification and provided the required PK samples through the final required PK sample relevant to the endpoint. The upper and lower ends of the boxes indicate the 25th and 75th quartiles, the triangles indicate the means, the horizontal lines within the boxes indicate the medians, and the error bars indicate 95% CIs.

AUC, area under the concentration-time curve; C, Cycle; CI, confidence interval; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous.

ORR and DoR

- ORR was noninferior between the SC and IV amivantamab arms
- DoR was 11.2 months in the SC arm vs 8.3 months in the IV arm, with twice as many patients, 29% in the SC arm vs 14% in the IV arm, having a response ≥6 months

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI)[a]		
All responders	30 (24–37)	33 (26–39)
	Relative risk, 0.92 (95% CI, 0.70–1.23); *P*=0.001	
Confirmed responders	27 (21–33)	27 (21–33)
	Relative risk, 0.99 (95% CI, 0.72–1.36); *P*<0.001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI)[b]	75 (69–81)	71 (64–77)
Median time to response (range), mo	1.5 (1.2–6.9)	1.5 (1.2–9.9)



[a]The objective response (CR or PR) was assessed using RECIST v1.1 and analyzed using logistic regression. The lower bound of the 95% CI indicated ≥70% retention of ORR exceeding the predefined 60% retention assumed for determining noninferiority. [b]Not protocol specified.

CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD); DoR, duration of response; IV, intravenous; mo, months; NE, not estimable; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous; SD, stable disease.

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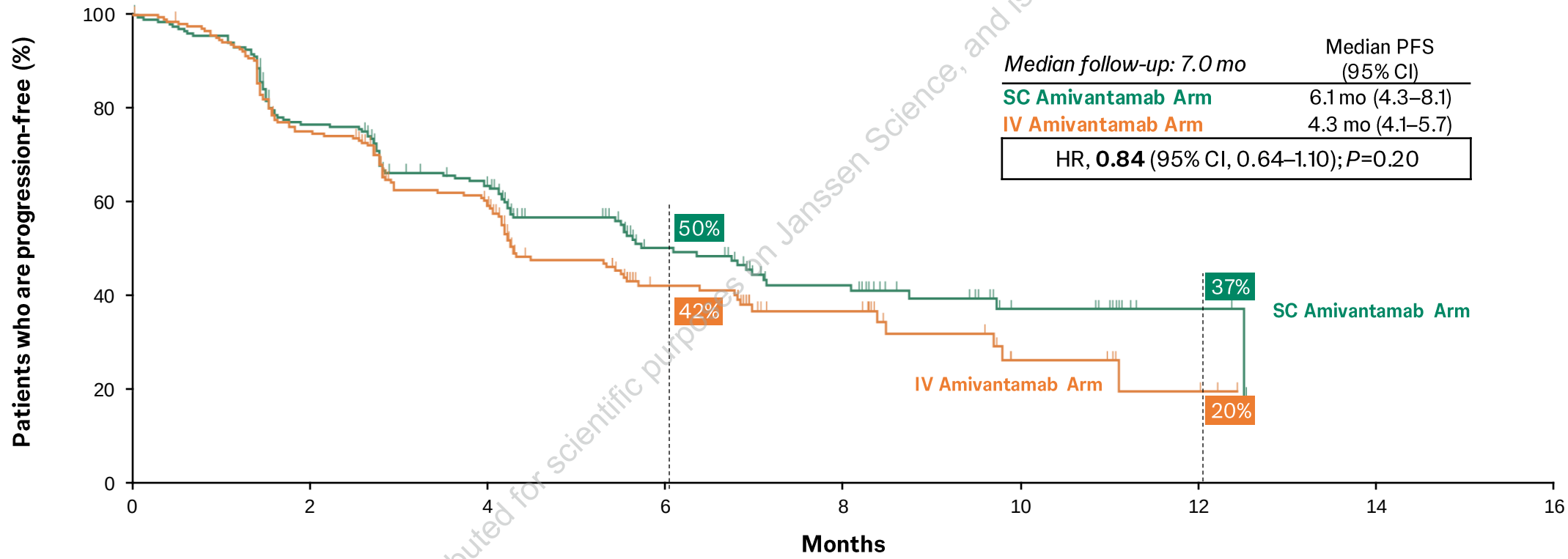
Progression-free Survival

PFS was numerically longer with SC vs IV amivantamab, with an HR of 0.84



No. at risk									
SC Amivantamab Arm	206	153	116	57	37	14	3	0	0
IV Amivantamab Arm	212	154	109	43	23	7	3	0	0

Note: The efficacy population included all the patients who had undergone randomization. PFS was tested for superiority as part of the hierarchical testing strategy; *P* value was calculated from a log-rank test stratified by history of brain metastases, Asian race, *EGFR* mutation type (Ex19del or L858R), and last line of therapy (osimertinib or platinum-based therapy).

CI, confidence interval; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; IV, intravenous; mo, months; PFS, progression-free survival; SC, subcutaneous.

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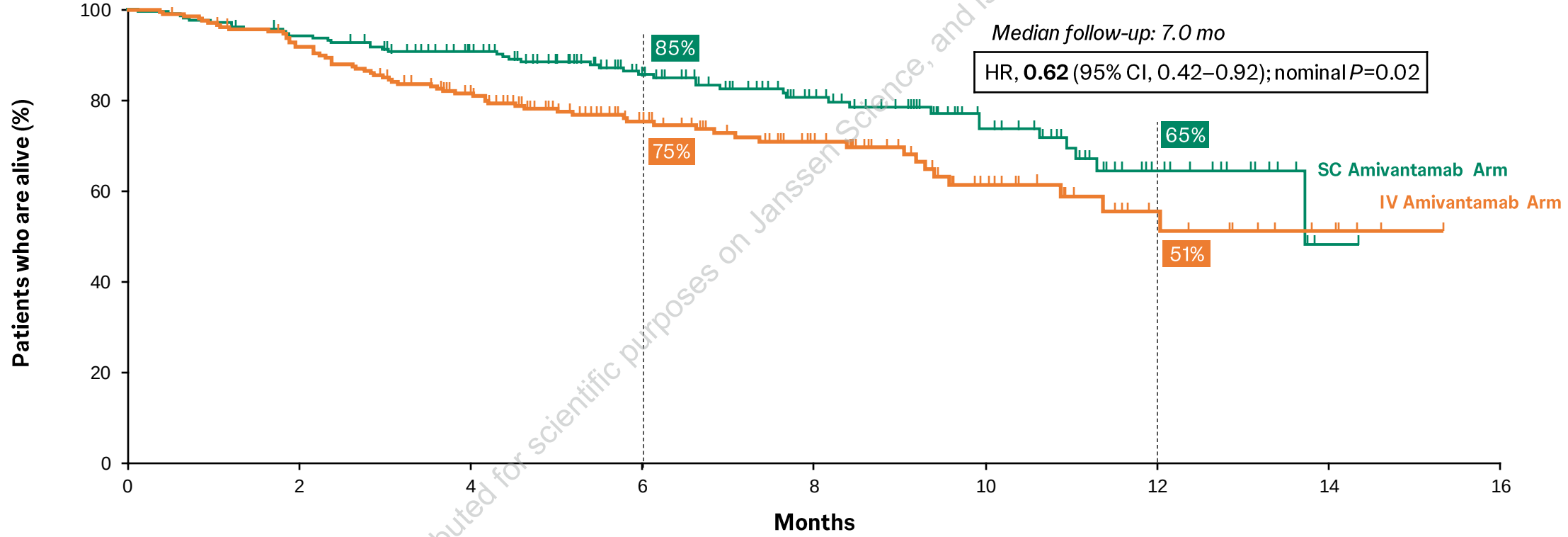
Overall Survival

There was an OS benefit associated with SC amivantamab, with an HR of 0.62 compared to the IV amivantamab arm[a]



No. at risk									
SC Amivantamab Arm	206	192	163	109	71	36	10	0	0
IV Amivantamab Arm	212	191	144	92	51	24	10	1	0

Note: The efficacy population included all the patients who had undergone randomization. [a]There were 43 deaths in the SC amivantamab arm and 62 deaths in the IV amivantamab arm. Nominal *P* value was calculated from a log-rank test stratified by history of brain metastases, Asian race, *EGFR* mutation type (Ex19del or L858R), and last line of therapy (osimertinib or platinum-based therapy); the prespecified endpoint was exploratory and not part of hierarchical hypothesis testing.

CI, confidence interval; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; IV, intravenous; mo, months; OS, overall survival; SC, subcutaneous.

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Summary of AEs

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=210)
Median treatment duration, mo (range)	4.7 (0.1–13.2)	4.1 (0–13.2)
Treatment-emergent AEs, n (%)		
Any AEs	204 (99)	209 (99)
Grade ≥3 AEs	107 (52)	118 (56)
Serious AEs	59 (29)	64 (30)
Any AE leading to death	7 (3)	10 (5)
Any AE leading to treatment		
Interruptions of any agent	127 (62)	127 (60)
Reductions of any agent	63 (31)	52 (25)
Discontinuations of any agent	26 (13)	29 (14)

- Treatment-emergent AEs were consistent between arms
- AEs leading to death were uncommon and similar between arms
- Treatment-related discontinuations: 9% in SC arm and 12% in IV arm

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.

AE, adverse event; IV, intravenous; mo, months; SC, subcutaneous.

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Safety Profile

Most common AEs were EGFR- and MET-related, majority grade 1-2, which is consistent with previous studies[1]

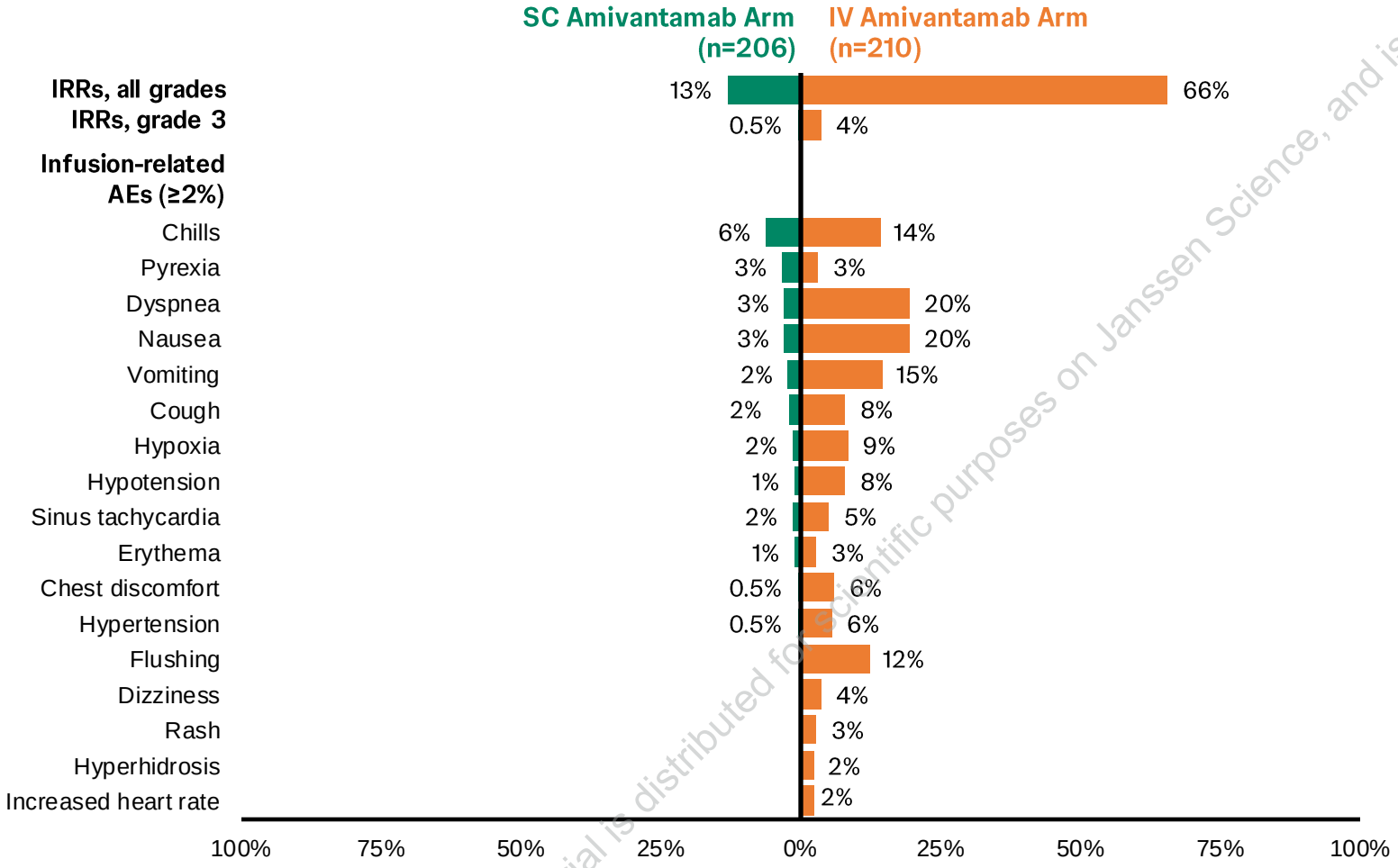
Most common AEs of any cause by preferred term (≥20%), n (%)	SC Amivantamab Arm (n=206)		IV Amivantamab Arm (n=210)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	111 (54)	8 (4)	108 (51)	3 (1)
Rash	95 (46)	8 (4)	91 (43)	8 (4)
Dermatitis acneiform	64 (31)	18 (9)	69 (33)	12 (6)
Stomatitis	57 (28)	1 (0.5)	69 (33)	5 (2)
Diarrhea	43 (21)	3 (1)	39 (19)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	96 (47)	9 (4)	77 (37)	8 (4)
Peripheral edema	52 (25)	6 (3)	58 (28)	1 (0.5)
Other				
Nausea	60 (29)	1 (0.5)	52 (25)	3 (1)
Increased ALT	46 (22)	6 (3)	56 (27)	8 (4)
Decreased appetite	45 (22)	1 (0.5)	52 (25)	3 (1)
Fatigue	44 (21)	3 (2)	43 (20)	5 (2)
Vomiting	44 (21)	2 (1)	41 (20)	1 (0.5)
Constipation	42 (20)	0	42 (20)	1 (0.5)
Headache	42 (20)	1 (0.5)	36 (17)	1 (0.5)
Increased AST	42 (20)	2 (1)	45 (21)	3 (1)
IRRs	27 (13)	1 (0.5)	138 (66)	8 (4)

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.

1. Cho BC, et al. Presented at the European Society for Medical Oncology Annual Meeting; October 20-24, 2023; LBA14.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; *EGFR*, epidermal growth factor receptor; MET, mesenchymal epithelial transition factor receptor; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous.

Incidence of IRR-related Symptoms



- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
  - There were no grade 4 or 5 IRRs
  - Most IRRs occurred during Cycle 1
- IRRs leading to hospitalization were not observed in the SC arm vs 2 events in the IV arm
- No IRR-related discontinuations occurred in the SC arm vs 4 events in the IV arm

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.
AE, adverse event; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous.

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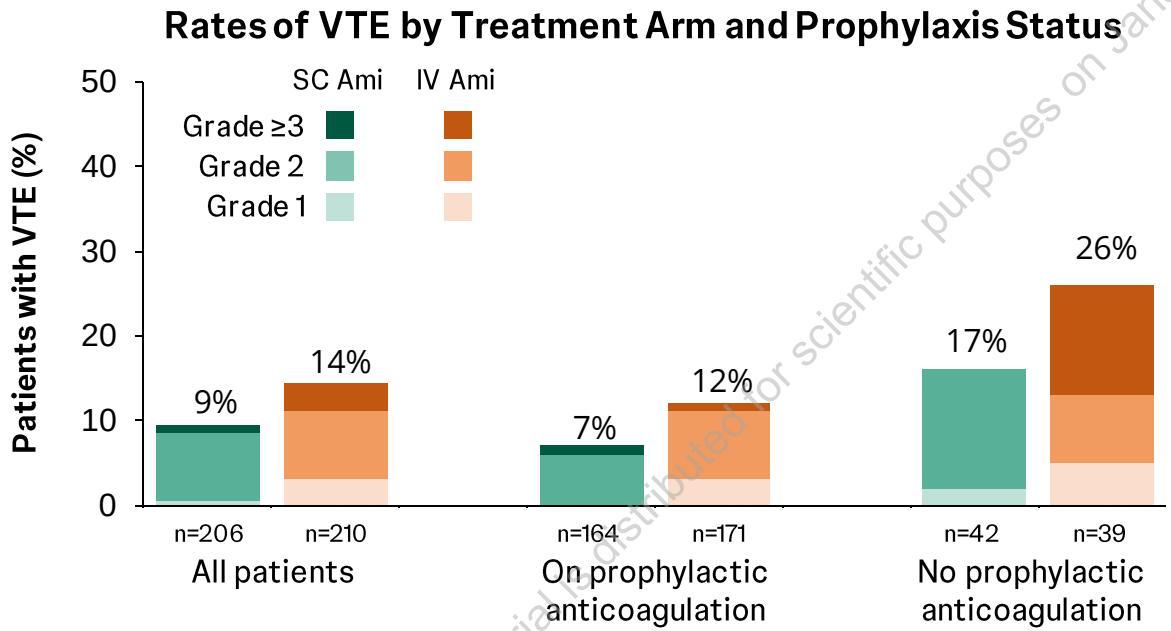
Adverse Event of Special Interest: VTE[a]

- Prophylactic anticoagulation[b] was administered to 80% (164/206) of patients in the SC arm and 81% (171/210) for IV
- Among all patients in the study, VTE was reported in 10% (32/335) of those receiving prophylactic anticoagulation vs 21% (17/81) who did not
- Rates of grade ≥3 bleeding events were uncommon in the SC (2%) and IV (1%) arms for those receiving prophylactic anticoagulation



- Between study arms, incidence of VTE was less frequent in the SC amivantamab arm compared to the IV arm, regardless of prophylactic anticoagulation status

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

[a]Grouping includes pulmonary embolism, deep vein thrombosis, venous embolism, venous thrombosis limb, embolism, thrombosis, subclavian vein thrombosis, superficial vein thrombosis, pulmonary infarction, venous thrombosis.
[b]VTE prophylaxis with apixaban, rivaroxaban, dalteparin, or enoxaparin was recommended by protocol (per the National Comprehensive Cancer Network guideline *Cancer-Associated Venous Thromboembolic Disease* v1.2022).

IV, intravenous; SC, subcutaneous; VTE, venous thromboembolism.

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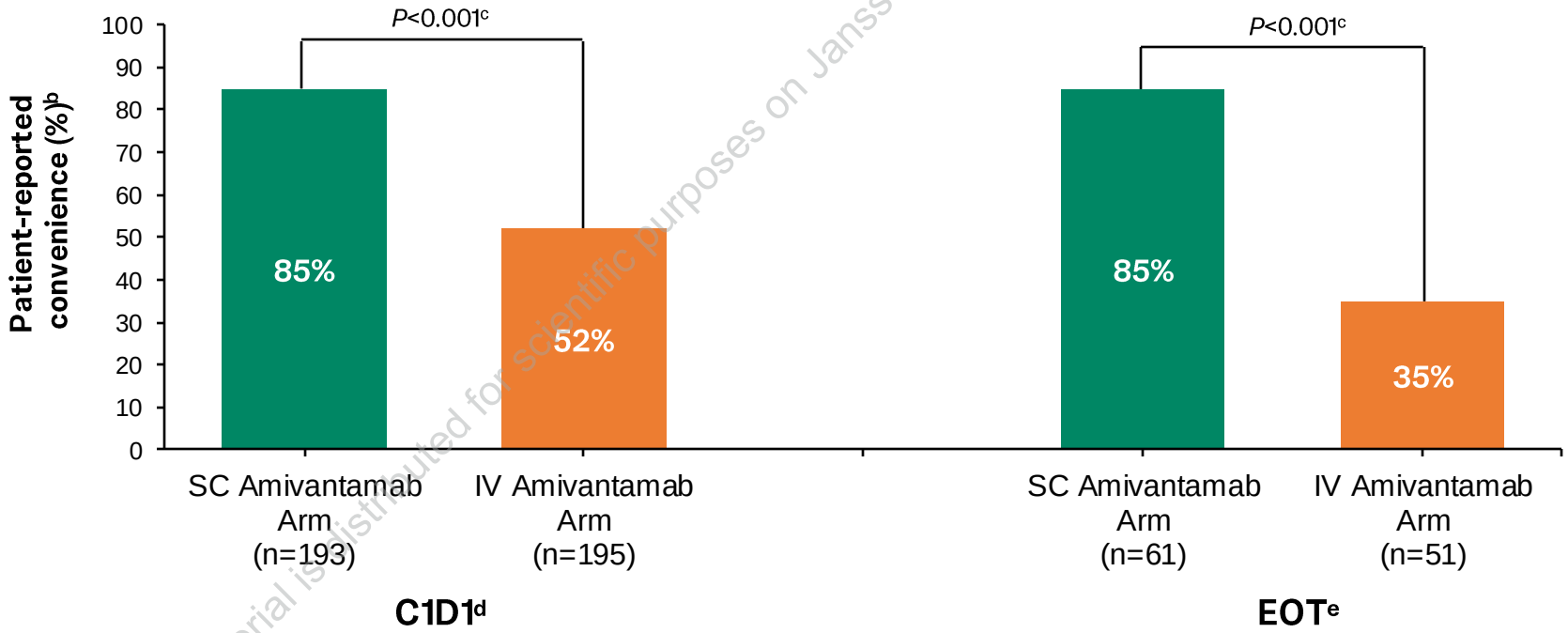
Treatment Administration Time and Convenience

- Treatment administration time was reduced to less than 5 minutes for SC amivantamab from 5 hours for the first infusion (2 hours for subsequent infusions) for IV amivantamab
- More patients reported their administration method to be convenient or very convenient with SC vs IV amivantamab

Frequency of Patient-reported Convenience per Modified TASQ[a]



[a]Response categories on the modified TASQ convenience question included "Very convenient", "Convenient", "Neither convenient nor inconvenient", "Inconvenient", and " Very Inconvenient". [b]Includes patients whose answer was "Very convenient" or "Convenient." [c]*P* values were nominal and obtained by Pearson's chi-squared test. [d]C1D2 for patients who received IV amivantamab due to split dosing. [e]Could have been collected after the last dose of treatment.
C, Cycle; D, Day; EOT, end of treatment; IV, intravenous; SC, subcutaneous; TASQ, Treatment Administration Satisfaction Questionnaire.

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Conclusions

- SC amivantamab + lazertinib demonstrated PK and ORR noninferiority to IV amivantamab + lazertinib in patients with *EGFR*-mutated advanced NSCLC with disease progression on or after osimertinib and chemotherapy
- Compared to the IV arm, SC amivantamab also showed:
  - Numerically longer DoR (11.2 vs 8.3 months) and PFS (6.1 vs 4.3 months)
  - Significant improvement in OS (HR, 0.62; nominal *P*=0.02)
- Future studies are needed to evaluate if SC absorption via the lymphatic system enhances amivantamab's immune-mediated activity
- The safety profile of SC amivantamab was consistent with IV, with fewer IRRs (13% vs 66%) and VTE (9% vs 14%)
- Administration time was substantially shorter for SC amivantamab (median <5 minutes) vs IV amivantamab (ranging from 2 to 5 hours), with significantly more patients reporting convenience (85% vs 35% at EOT)

SC amivantamab + lazertinib provided noninferior efficacy, lower rates of IRRs and VTE, and is more convenient for patients and providers vs IV amivantamab + lazertinib

DoR, duration of response; EGFR, epidermal growth factor receptor; EOT, end of treatment; HR, hazard ratio; IRR, infusion-related reaction; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; SC, subcutaneous; VTE, venous thromboembolism.

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Also at ASCO 2024

MARIPOSA

Amivantamab + lazertinib vs osimertinib in **first-line *EGFR*-mutated** advanced NSCLC with **biomarkers of high-risk** disease

Abstract 8504: May 31 at 3:57pm (Arie Crown Theater)

CHRYSALIS-2

Amivantamab + lazertinib in **atypical *EGFR*-mutated** advanced NSCLC (CHRYSALIS-2)

Abstract 8516: June 1 at 5:00pm (S406)

METalmark

Amivantamab + capmatinib in advanced NSCLC harboring *MET* alterations

Abstract 8619: June 3 at 1:30pm (Hall A)

PALOMA-2

Amivantamab + lazertinib in **first-line *EGFR*-mutated** advanced NSCLC (MARIPOSA population)

LBA 8612: June 3 at 1:30pm (Hall A)

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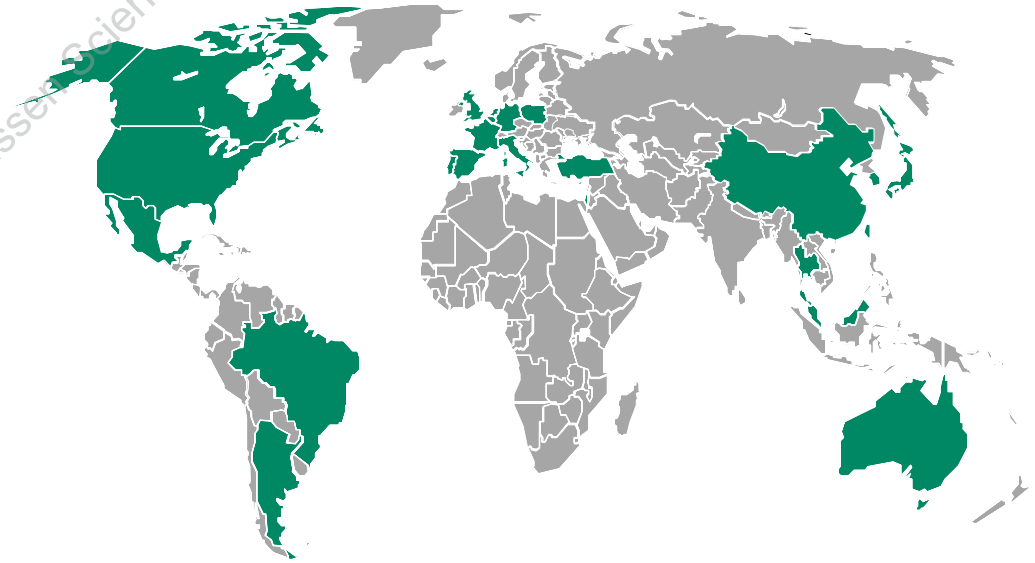
Acknowledgments

- Patients who participated in the study and their families and caregivers
- Physicians and nurses who cared for patients and staff members who supported this clinical trial
- Staff members at the study sites and involved in data collection/analyses
- Medical writing assistance was provided by Lumanity Communications Inc. and funded by Janssen Global Services, LLC

A total of 418 patients from 20 countries were randomized in the PALOMA-3 study



https://www.congresshub.com/Oncology/AM2024/Amivantamab/Leighl