Subcutaneous Amivantamab and Lazertinib as First-line Treatment in Patients with *EGFR*-mutated Advanced Non-small Cell Lung Cancer (NSCLC): Interim Results From the Phase 2 PALOMA-2 Study

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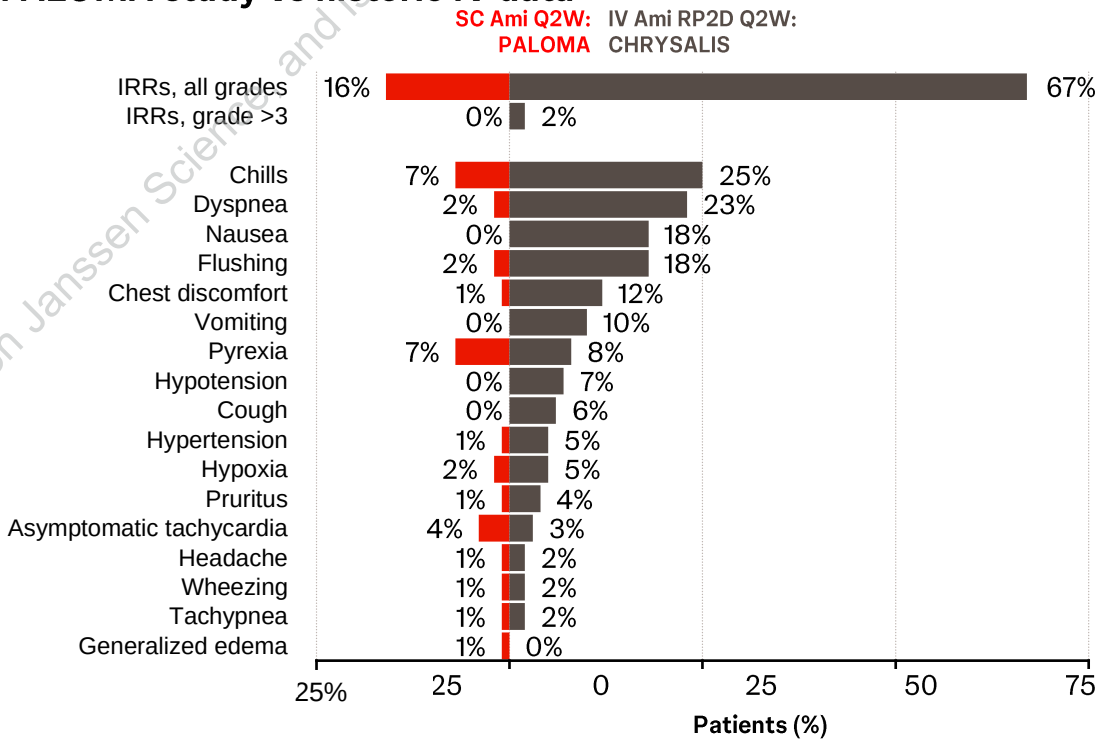
BACKGROUND

- Amivantamab, an EGFR–MET bispecific antibody with immune cell–directing activity,[1-3] is approved as an IV formulation for the first- and second-line treatment of patients with *EGFR* Ex20ins–mutated advanced NSCLC[4-6]
- In the MARIPOSA study, first-line amivantamab + lazertinib (a third-generation EGFR-TKI) demonstrated superior PFS vs osimertinib in patients with *EGFR* Ex19del– or L858R-mutated advanced NSCLC (23.7 vs 16.6 months, respectively; HR, 0.70; *P*<0.001)[7]
- The SC formulation is expected to improve the overall patient experience and health care provider convenience
- In the phase 1 PALOMA study (ClinicalTrials.gov Identifier: NCT04606381), SC amivantamab was associated with a low rate (16%) of IRRs (**Figure 1**) and short administration times (≤7 minutes for the Q2W and Q3W dosing regimens and 10 minutes for the Q4W regimen)[8,9]

Figure 1: Incidence of IRRs and IRR-related symptoms in the phase 1 PALOMA study vs historic IV data[8]



PALOMA-2 (ClinicalTrials.gov Identifier: NCT05498428) evaluated the efficacy, safety, and PK of first-line SC amivantamab + lazertinib in *EGFR*-mutated advanced NSCLC

ami, amivantamab; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; Ex20ins, exon 20 insertion; HR, hazard ratio; IRR, infusion-related reaction; IV, intravenous; MET, mesenchymal epithelial transition factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every 2 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous; TKI, tyrosine kinase inhibitor.

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. *J Clin Oncol.* 2021;39(30):3391-3402. 6. Zhou C, et al. *N Engl J Med.* 2023;389(22):2039-2051. 7. Cho BC, et al. *Ann Oncol.* 2023;34:S1306. 8. Minchom AR, et al. *J Clin Oncol.* 2023;41(16 suppl):9134. 9. Leighl N, et al. Presented at: European Lung Cancer Congress (ELCC) Annual Meeting; March 20–23, 2024; Prague, Czech Republic.

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METHODS

- PALOMA-2 is a global, parallel-cohort, phase 2 study evaluating the efficacy, safety, and PK of SC amivantamab (including combinations with chemotherapy and/or lazertinib) in patients with locally advanced or metastatic *EGFR*-mutated NSCLC
- Cohorts 1 and 6 enrolled patients with treatment-naïve, *EGFR* Ex19del– or L858R-mutated NSCLC (**Figure 2**)
  - SC amivantamab, co-formulated with hyaluronidase (rHuPH20) was administered by manual injection in the abdomen at 1600 mg (or 2240 mg if ≥80 kg) weekly for the first 4 weeks and Q2W thereafter
  - Lazertinib was administered orally at 240 mg daily
  - Prophylactic anticoagulation for the first 4 months of treatment was recommended in Cohort 1 and required in Cohort 6
- The primary endpoint was ORR as assessed by the investigator per RECIST v1.1
- ARRs were defined as *Medical Dictionary for Regulatory Activities* preferred term "Administration Related Reaction" (referred to as IRRs in prior studies)
- Time to ARR onset was calculated as the start of the ARR minus the start of the last injection prior to this event
- 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)

ARR, administration-related reaction; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; IRR, infusion-related reaction; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; PK, pharmacokinetics; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous; VTE, venous thromboembolism.

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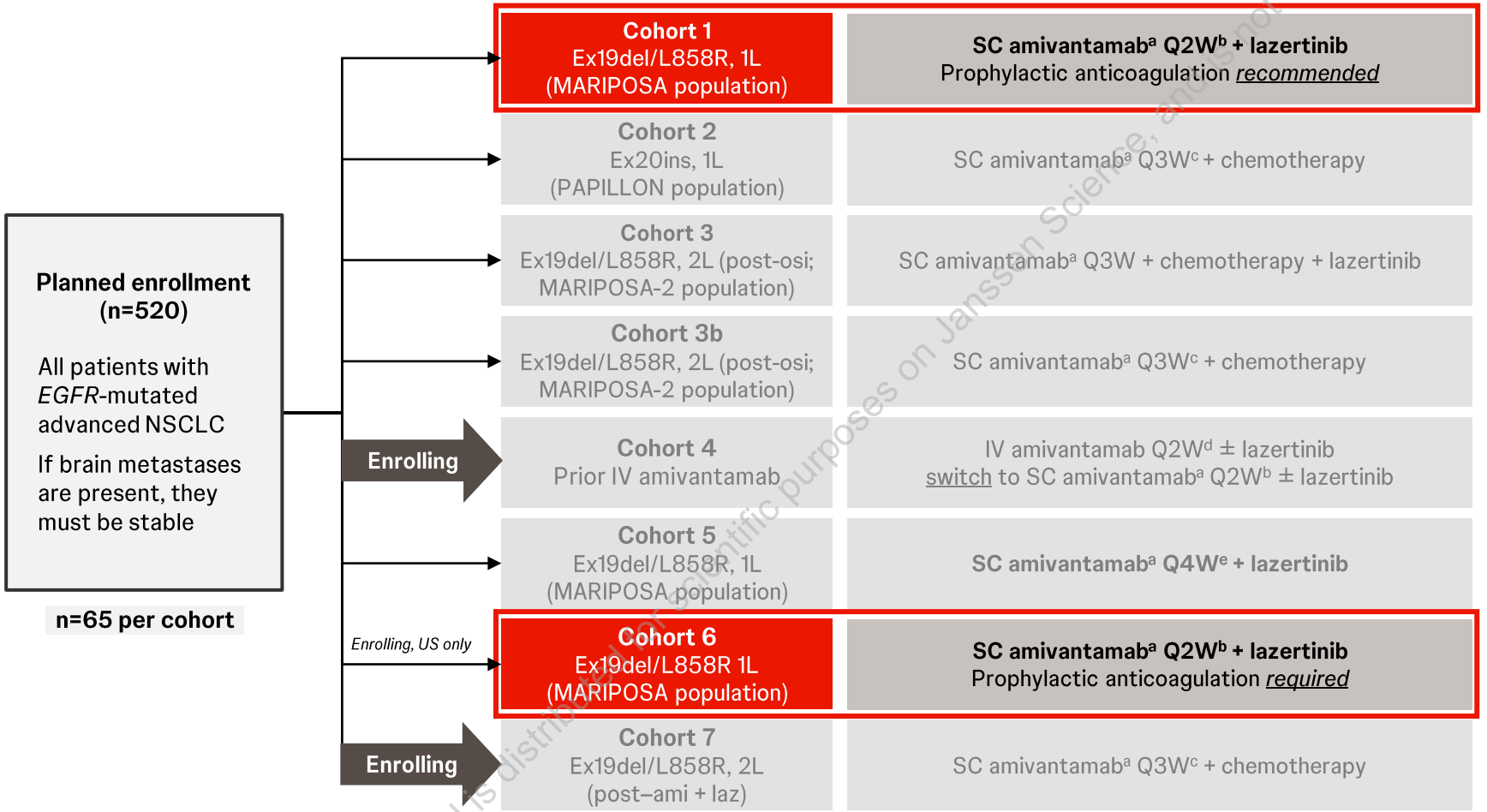
FIGURE 2: PALOMA-2 Study Design



Focus of this presentation

Primary endpoint[f]:

- ORR by INV

Secondary endpoints:

- ORR by ICR
- DoR
- TTR
- CBR
- PFS
- OS
- Safety
- PK

Focus of this presentation

[a]SC amivantamab was administered by manual injection in the abdomen. [b]SC amivantamab Q2W dose: 1600 mg (2240 mg if ≥80 kg). [c]SC amivantamab Q3W dose: 2400 mg (3360 mg if ≥80 kg). [d]IV amivantamab Q2W dose (1050 mg or 1400 mg if ≥80 kg). [e]SC amivantamab Q4W dose: 3520 mg (4640 mg if ≥80 kg). [f]The primary endpoint for Cohort 4 is safety and secondary endpoint is PRO.

1L, first line; 2L, second line; C, cycle; CBR, clinical benefit rate; DoR, duration of response; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion mutation; Ex20ins, Exon 20 insertion mutation; ICR, independent central review; INV, investigator; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; osi, osimertinib; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous; TTR, time to response.

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RESULTS: Demographic and Baseline Characteristics

- As of January 6, 2024, 68 and 58 patients were enrolled in Cohorts 1 and 6, respectively (**Table 1**)
  - The median follow-up was 10.0 months for Cohort 1 and 6.1 months for Cohort 6
  - As of the data cutoff, 75% of patients in Cohort 1 and 93% of patients in Cohort 6 were still undergoing treatment

Table 1: Demographic and baseline disease characteristics

Characteristic	Cohort 1 (n=68)	Cohort 6 (n=58)	Overall (N=126)
Median age (range), years	58 (28–85)	62 (34–83)	59 (28–85)
Female, n (%)	42 (62)	34 (59)	76 (60)
Race, n (%)			
Asian	45 (66)	40 (69)	85 (67)
White	19 (28)	16 (28)	35 (28)
Other[a]	4 (6)	2 (3)	6 (5)
ECOG PS score of 1, n (%)	48 (71)	43 (74)	91 (72)
History of smoking, n (%)	15 (22)	18 (31)	33 (26)
Brain metastases, n (%)	20 (29)	18 (31)	38 (30)
EGFR mutation type,[b] n (%)			
Ex19del	45 (66)	34 (59)	79 (63)
L858R	24 (35)	24 (41)	48 (38)
Adenocarcinoma histology, n (%)	65 (96)	57 (98)	122 (97)

[a]Other includes Black or African American and American Indian or Alaska Native. [b]Patients could be included in >1 category.

ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epithelial growth factor receptor; Ex19del, Exon 19 deletion.

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RESULTS: Efficacy

Table 2: Responses (confirmed and unconfirmed)

	Cohort 1 (n=68)		Cohort 6 (n=45)[a]		Overall (N=113)	
	INV	ICR	INV	ICR	INV	ICR
ORR, % (95% CI)	75 (63–85)	81 (70–89)	80 (65–90)	76 (61–87)	77 (68–84)	79 (70–86)

The median follow-up was 10.0 months for Cohort 1, 6.1 months for Cohort 6, and 8.6 months overall

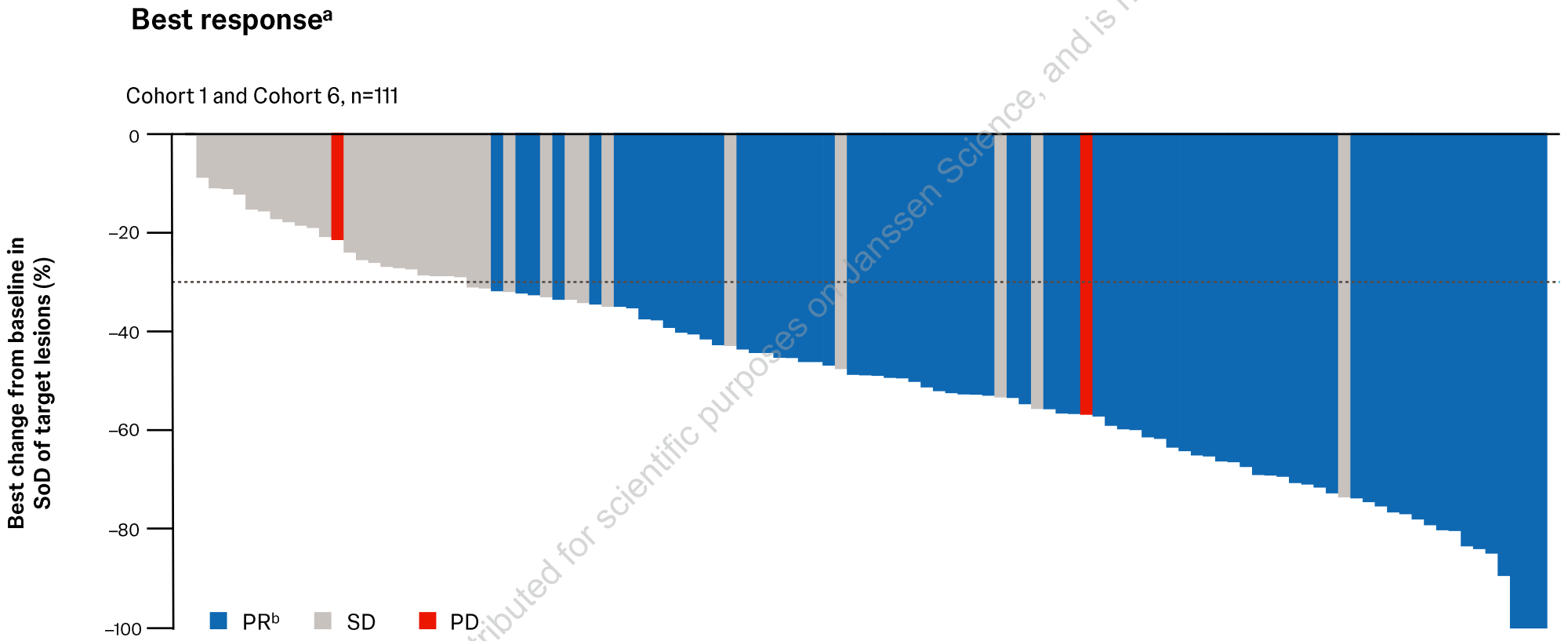
- Among all patients, the INV-assessed ORR was 77% and the ICR-assessed ORR was 79% (**Table 2**)
  - A similar BICR-assessed ORR of 86% (95% CI, 83–89) was observed with IV amivantamab + lazertinib in MARIPOSA[1]
- Among confirmed responders in both cohorts (**Figure 3**):
  - Median time to response was 1.9 months (range, 1.4–5.3)
  - Median DoR was not estimable

[a]Efficacy analyses in Cohort 6 were performed on patients who enrolled on or before July 20, 2023.

1. Cho BC, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; October 20–24, 2023; Madrid, Spain.

BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; ICR, independent central review; INV, investigator; ORR, objective response rate.

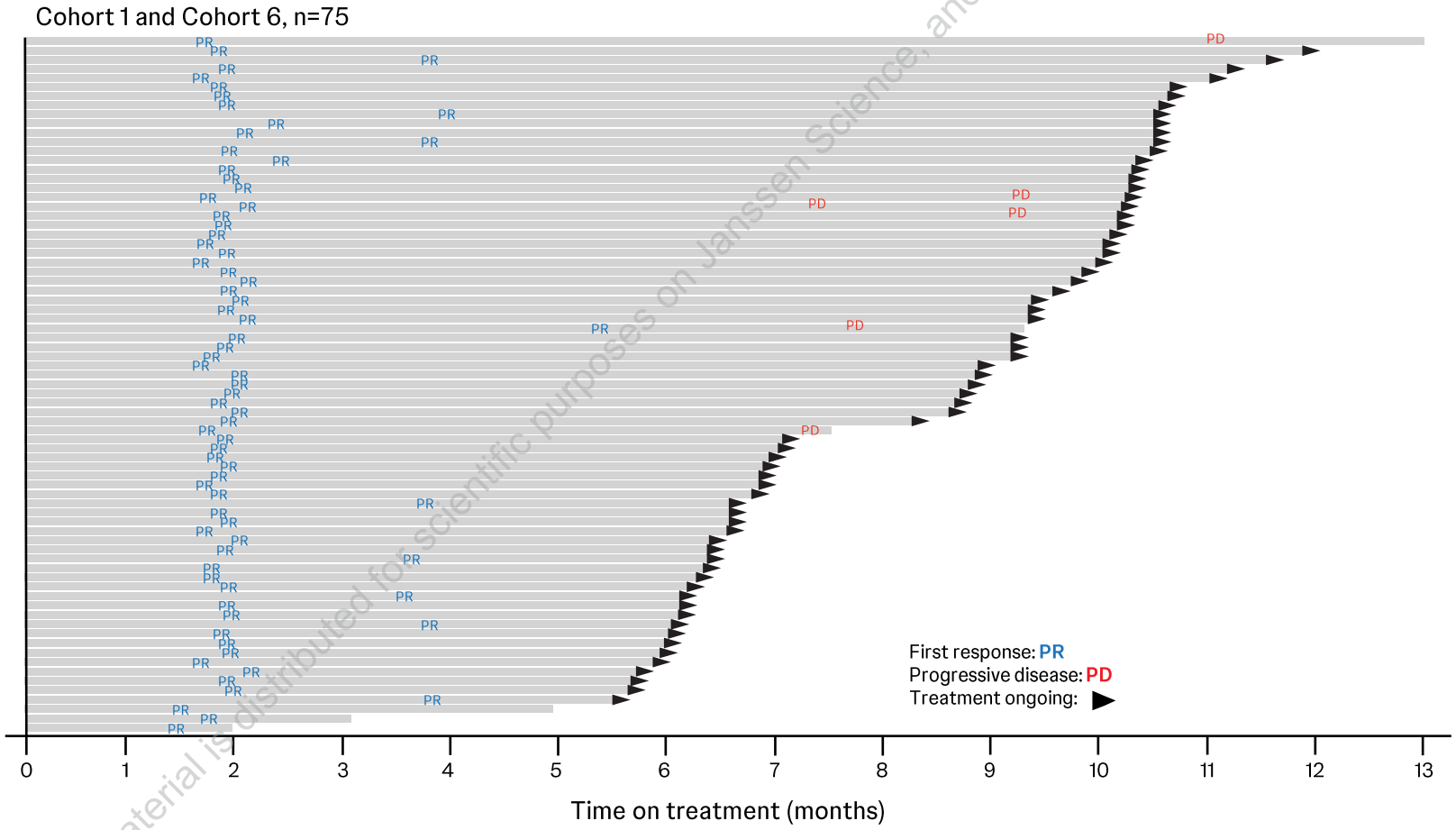
RESULTS: Figure 3A



[a]Patients without post-baseline tumor assessment were not included. [b]Including confirmed responders only.
PD, progressive disease, PR, partial response; SD, stable disease; SoD, sum of diameters.

RESULTS: Figure 3B

DoR[a] in confirmed responders



[a]Patients without post-baseline tumor assessment were not included.

DoR, duration of response; PD, progressive disease, PR, partial response.

RESULTS: Safety

- Aside from markedly lower rates of ARRs and VTE, the safety profile of SC amivantamab + lazertinib was consistent with what was previously reported with IV amivantamab + lazertinib,[1,2] with no new safety signals identified (**Table 3**)
  - Discontinuations of all agents due to treatment-related AEs occurred in 9% (11/125) of patients
- ARRs were reported by 15% (19/125) of patients
  - The majority of ARRs (n=18/20; 90%) occurred in Cycle 1 (on or after Cycle 1 Day 1 but before the next dose); one patient experienced 2 ARRs (one on Cycle 1 Day 1 and one on Cycle 1 Day 9)
  - Median time to ARR onset was 2.3 hours (range, 0.3–7.2)
  - The rate was lower compared with the rate with IV administration in MARIPOSA (63%)[1]

Table 3: Safety profile

Most common treatment-emergent AEs (≥20%), n (%)	Cohort 1 (n=68)		Cohort 6 (n=57)[a]		Overall (N=125)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition						
Paronychia	49 (72)	2 (3)	40 (70)	2 (4)	89 (71)	4 (3)
Rash	48 (71)	9 (13)	28 (49)	3 (5)	76 (61)	12 (10)
Dermatitis acneiform	31 (46)	10 (15)	18 (32)	1 (2)	49 (39)	11 (9)
Pruritus	22 (32)	0	15 (26)	0	37 (30)	0
Stomatitis	20 (29)	3 (4)	31 (54)	1 (2)	51 (41)	4 (3)
Diarrhea	16 (24)	0	12 (21)	1 (2)	28 (22)	1 (1)
Associated with MET inhibition						
Hypoalbuminemia	37 (54)	3 (4)	23 (40)	0	60 (48)	3 (2)
Peripheral edema	26 (38)	1 (1)	14 (25)	1 (2)	40 (32)	2 (2)
Other						
Increased ALT	26 (38)	0	21 (37)	3 (5)	47 (38)	3 (2)
Increased AST	22 (32)	1 (1)	19 (33)	2 (4)	41 (33)	3 (2)
Nausea	16 (24)	0	16 (28)	0	32 (26)	0
Decreased appetite	18 (26)	0	13 (23)	0	31 (25)	0
Myalgia	18 (26)	1 (1)	12 (21)	0	30 (24)	1 (1)
Constipation	18 (26)	0	14 (25)	0	32 (26)	0
Paresthesia	14 (21)	0	6 (11)	0	20 (16)	0

[a]One patient in Cohort 6 was enrolled but not treated at the time of the data cutoff.

1. Cho BC, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; October 20–24, 2023; Madrid, Spain. 2. Lee SH, et al. *J Clin Oncol.* 2023;41(16_suppl):9134.

AE, adverse event; ALT, alanine aminotransferase; ARR, administration-related reaction; AST, aspartate aminotransferase; EGFR, epithelial growth factor receptor; IV, intravenous; MET, mesenchymal epithelial transition; SC, subcutaneous; VTE, venous thromboembolism.

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RESULTS: Safety (VTE)

- A total of 71% (48/78) of patients in Cohort 1 and all patients in Cohort 6 received prophylactic anticoagulation
- Overall, VTE was reported in 18% (12/68) and 7% (4/57) of patients in Cohorts 1 and 6, respectively (13% [16/125] of all patients; **Table 4**)
  - There were no dose reductions or discontinuations due to VTE
- Among 12 patients who developed VTE in the prophylactic anticoagulation group, 11 (92%) developed VTE after discontinuing prophylactic anticoagulation
  - The median VTE onset time after stopping prophylactic anticoagulation was 70 days (range, 2–185)
- Grade ≥3 bleeding was reported in 2% (2/105) of patients with prophylactic anticoagulation use

Table 4: VTE[a] and bleeding events[b] based on prophylactic anticoagulation use

	Prophylactic anticoagulation (n=105)	No prophylactic anticoagulation (n=20)	Total (n=125)
Any VTE, n (%)	12 (11)[c]	4 (20)	16 (13)
Grade ≥3	0	1 (5)	1 (1)
Grade 5	0	0	0
Any VTE leading to death, n (%)	0	0	0
Any VTE leading to any discontinuation, n (%)	0	0	0
Grade ≥3 bleeding, n (%)	2 (2)[d]	0	2 (2)

[a]VTE AEs were identified by the SMQ for "Embolic and thrombotic events, venous" and the preferred term is "Thrombosis" or "Embolism." [b]Bleeding AE terms were identified by the standardized MedDRA query for "Hemorrhage terms (excl laboratory terms)" (narrow scope). [c]Among 12 patients who developed VTE in the prophylactic anticoagulation group, 11 (92%) developed VTE after using prophylactic anticoagulation, with a median VTE onset time of 70 days (range, 2–185) after stopping. [d]One patient had been on 10 mg of oral rivaroxaban daily since Day 1 and developed grade 3 chronic pigmented purpura on Day 67, which resolved on Day 79. One patient had been on 10 mg of oral rivaroxaban daily since Day 1 and developed grade 3 subarachnoid hemorrhage on Day 76, which remained unresolved.

AE, adverse event; excl, excluding; MedDRA, *Medical Dictionary for Regulatory Activities*; SMQ, Standardized MedDRA Query; VTE, venous thromboembolism.

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RESULTS: Pharmacokinetics

- Consistent with historic IV levels (317 [32] µg/mL), mean (%CV) amivantamab trough concentrations on Cycle 2 Day 1 were:
  - 328 (32) µg/mL (n=50) in Cohort 1
  - 373 (27) µg/mL (n=42) in Cohort 6

CV, coefficient of variation; IV, intravenous.

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CONCLUSIONS

- SC amivantamab + lazertinib showed meaningful efficacy in first-line *EGFR*-mutated advanced NSCLC, with an ORR comparable to that of IV amivantamab + lazertinib in the MARIPOSA study[1]
- Overall, the safety profile of SC amivantamab + lazertinib was similar to MARIPOSA, except for ARRs (15%, all grade 1-2) and VTE (13%, most grade 1-2), which were markedly lower than IV (63% and 37% in MARIPOSA, respectively)
- Prophylactic anticoagulation can be safely implemented and effectively reduces the rates of VTE among patients treated with amivantamab + lazertinib
- Consistent PK profiles further support the use of SC amivantamab + lazertinib

1. Cho BC, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; October 20–24, 2023; Madrid, Spain. 2. Leighl N, et al. Presented at: European Lung Cancer Congress (ELCC) Annual Meeting; March 20–23, 2024; Prague, Czech Republic.

ARR, administration-related reaction; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; PK, pharmacokinetic; Q2W, every 2 weeks; SC, subcutaneous; VTE, venous thromboembolism.

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KEY TAKEAWAY

- This bridging study provided promising evidence for the efficacy and safety of subcutaneous amivantamab + lazertinib and suggested that subcutaneous amivantamab + lazertinib could be a valuable first-line treatment option for patients with *EGFR*-mutated advanced NSCLC

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

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Disclosures

JLT received honoraria for lectures/presentations from MSD, Boehringer Ingelheim, and Pfizer; and received support for attending meetings from MSD. **JMD** serves in a consulting or advisory role for AstraZeneca and MSD; participated in a speakers bureau for AstraZeneca, Amgen, Janssen, Roche, and Sanofi; received support for travel from Amgen and Janssen; and received research funding for his institution from Bristol Myers Squibb Brazil, Merck, Ipsen, Novartis, Roche, Janssen, MSD, Amgen, BeiGene, and Debiopharm. **SHH** received travel support from MSD; received honoraria from Roche, MSD, and AstraZeneca; and received research funding from AstraZeneca, MSD Oncology, Novartis, and Janssen Oncology. **BM** serves in a consulting or advisory role for Roche, Boehringer Ingelheim, AstraZeneca, Merck Serono, and Janssen; participated in a speakers bureau for Roche, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Sanofi/Regeneron, Janssen Oncology, and Pfizer; and received travel support from Roche, MSD Oncology, and AstraZeneca. **LM** received travel support from Roche. **MN** serves in a consulting or advisory role for AstraZeneca, Caris Life Sciences, Daiichi Sankyo, EMD Serono, Genentech, Janssen, Eli Lilly, Mirati Therapeutics, Novartis, Pfizer, and Takeda; participated in a speakers bureau for Blueprint Medicines, Janssen, Mirati Therapeutics, and Takeda; received research funding from Tempus; and received travel support from AnHeart Therapeutics. **DV** received honoraria from AstraZeneca; serves in a consulting or advisory role for Bristol Myers Squibb, MSD Oncology, Roche/Genentech, Pfizer, AstraZeneca, Boehringer Ingelheim, Gilead/Forty Seven, and Novartis; and received travel support from AstraZeneca. **NG** received consulting fees or honoraria from AbbVie, Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Hoffmann–La Roche, Janssen, Leo Pharma, Eli Lilly, MSD, Novartis, Sivan, Mirati Therapeutics, Pfizer, Sanofi, and Takeda; received support for attending meetings from Janssen, Amgen, and Bristol Myers Squibb; and participated on a data safety monitoring board or advisory board for Hoffman–La Roche. **AR** serves in a consulting or advisory role for Eli Lilly, Roche/Genentech, Boehringer Ingelheim, MSD, Bristol Myers Squibb, AstraZeneca/MedImmune, Pfizer, AbbVie, Novartis, and GSK; and participated on a speakers bureau for Roche/Genentech, Eli Lilly, Bristol Myers Squibb, MSD, and Novartis. **D-AB**, **AA**, **JM**, **JZ**, **JMB**, and **MB** are employees and shareholders of Janssen. **SCS** serves in a consulting or advisory role for Amgen, AstraZeneca, Foundation Medicine, Genentech/Roche, Janssen, Regeneron, and Tempus; and received research funding from Mirati Therapeutics, Bristol Myers Squibb, and Janssen. **SML**, **PJV**, **XZ**, and **HX** have no conflicts of interest to disclose.

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