Subcutaneous amivantamab plus chemotherapy in *EGFR*-mutant advanced non-small cell lung cancer after disease progression on osimertinib

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Presented by E Nadal at the European Society for Medical Oncology (ESMO) Congress; October 17–21, 2025; Berlin, Germany

Background

- Amivantamab, an EGFR-MET bispecific antibody with immune cell–directing activity, is approved as an IV formulation in combination with chemotherapy for *EGFR*-mutated advanced NSCLC after disease progression on EGFR-TKIs[1–6]
  - In MARIPOSA-2 (ClinicalTrials.gov Identifier: NCT04988295; median follow-up, 8.7 months), amivantamab IV Q3W + chemotherapy demonstrated a BICR-assessed PFS of 6.3 months (95% CI, 5.6–8.4) and ORR of 64%[1]
- In PALOMA-3 (ClinicalTrials.gov Identifier: NCT05388669), SC amivantamab Q2W + lazertinib demonstrated noninferior PK and efficacy to amivantamab IV Q2W + lazertinib
  - Amivantamab SC also showed fewer IRRs (13% vs 66%), shorter administration time (4.8 min vs 5.0 h), higher patient convenience (85% vs 35% at end of treatment), and reduced medical resource utilization, leading to its approval by the European Commission[7–9]
- The phase 2 PALOMA-2 study (ClinicalTrials.gov Identifier: NCT05498428) is a bridging study evaluating amivantamab SC–based regimens in various *EGFR*-mutated advanced NSCLC settings

Here, we report the efficacy, safety, and pharmacokinetics of amivantamab SC Q3W + chemotherapy in participants with *EGFR*-mutated NSCLC after disease progression on osimertinib

BICR, blinded independent central review; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks; SC, subcutaneous; TKI, tyrosine-kinase inhibitor.

1. Passaro A, et al. *Ann Oncol*. 2024;35(1):77–90. 2. Moores SL, et al. *Cancer Res*. 2016;76(13):3942–3953. 3. Vijayaraghavan S, et al. *Mol Cancer Ther*. 2020;19(10):2044–2056. 4. Yun J, et al. *Cancer Discov*. 2020;10(8):1194–1209. 5. RYBREVANT® (amivantamab-vmjw) injection for intravenous use [package insert]. Janssen Biotech, Inc; 2025. 6. RYBREVANT®: EPAR [product information]. Janssen-Cilag International NV; 2024. 7. Leighl NB, et al. *J Clin Oncol*. 2024;42(30):3593-3605. 8. Alexander M, et al. *Eur J Cancer*. 2025 Jul 10;227:115624. 9. Johnson & Johnson. European Commission approves subcutaneous RYBREVANT® (amivantamab) for the treatment of patients with advanced *EGFR*-mutated non-small cell lung cancer. April 7, 2025. Accessed July 31, 2025.

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Methods

- Cohort 3b enrolled participants with locally advanced or metastatic *EGFR*-mutated (exon 19 deletions or L858R substitutions) NSCLC who have experienced disease progression on or after osimertinib monotherapy (as the most recent line; **Figure 1**)
- The primary endpoint was ORR as assessed by INV per Response Evaluation Criteria in Solid Tumors v1.1
- "Administration-related reaction" was defined per the *Medical Dictionary for Regulatory Activities* preferred term (referred to as IRRs in prior IV studies)

EGFR, epidermal growth factor receptor; INV, investigator; IRR, infusion-relation reaction; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate.

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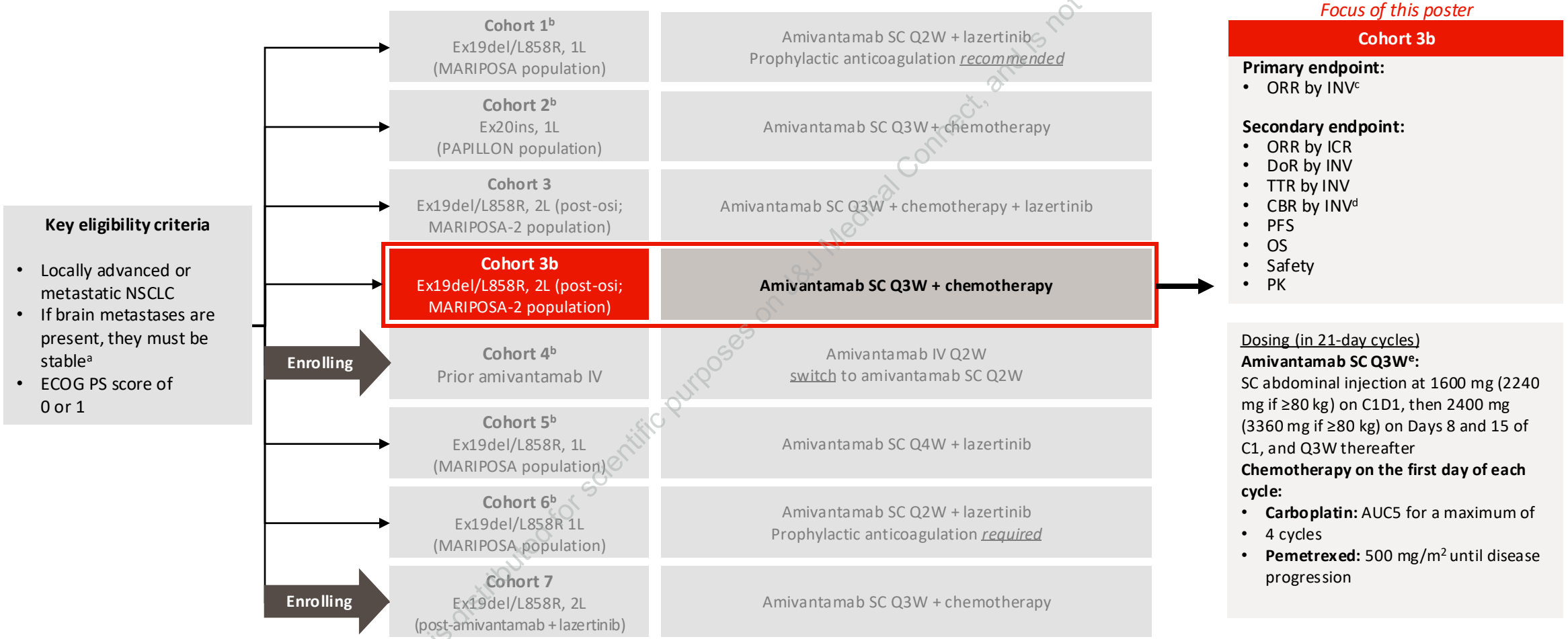
Figure 1: PALOMA-2 study design



[a]Includes asymptomatic or previously treated participants with stable brain metastases. [b]Results from these cohorts have been previously presented.[1-4] [c]Tumor response was assessed according to RECIST v1.1. [d]CBR was defined as confirmed response or stable disease for ≥11 weeks. [e]Coformulated with recombinant human hyaluronidase PH20 and manually injected in the abdomen.

1L, first-line; 2L, second-line; AUC5, area under the curve of 5; C, Cycle; CBR, clinical benefit rate; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; Ex19del, exon 19 deletion; Ex20ins, exon 20 insertion; 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; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous; TTR, time to response.

1. Lim SM, et al. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA. 2. Lim SM, et al. Presented at the European Lung Cancer Congress (ELCC); March 26–29, 2025; Paris, France. 3. Lim SM, et al. Presented at the World Conference on Lung Cancer (WCLC) Annual Meeting; September 6–9, 2025; Barcelona, Spain. 4. Scott SC, et al. Presented at the WCLC Annual Meeting; September 6–9, 2025; Barcelona, Spain.

Results: Baseline demographic and clinical characteristics

- Cohort 3b enrolled a total of 77 participants whose disease had progressed on prior osimertinib (**Table 1**)
- As of October 24, 2024, median follow-up was 7.0 months and median treatment duration was 6.2 months
  - As of the data cutoff, 48 (62%) participants were still ongoing treatment

Table 1: Baseline demographic and clinical characteristics

Characteristic, n (%)	Cohort 3b (N=77)
Median age (range), years	63 (41–77)
Female	44 (57)
Race	
Asian	38 (49)
White	37 (48)
Black or African American	2 (3)
ECOG PS score of 1	45 (58)
History of smoking	27 (35)
Brain metastases	27 (35)
***EGFR* mutation type[a]**	
Ex19del	44 (57)
L858R	33 (43)

[a]Participants can be included in ≥1 category.
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion.

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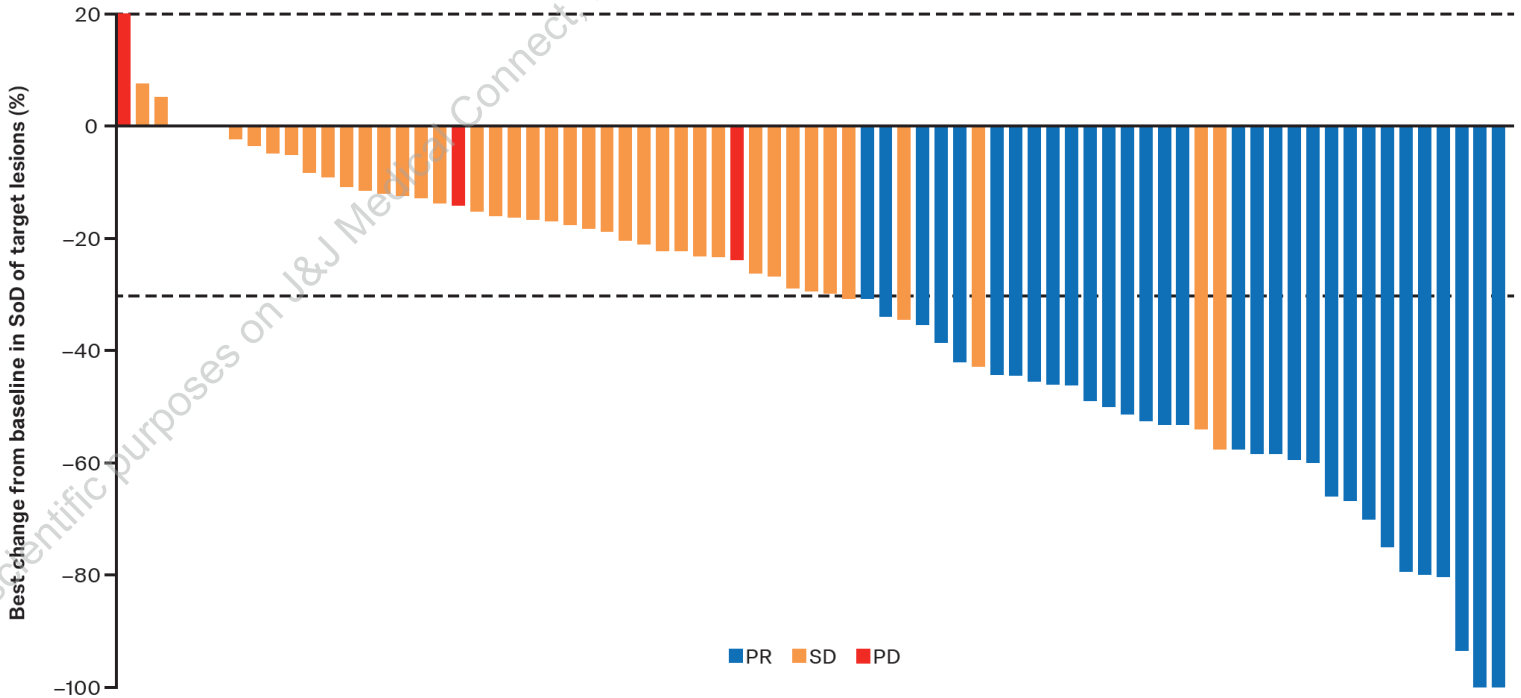
Results: Efficacy

- Among all participants, ORR was 47% (95% CI, 35–59) by INV and 53% (95% CI, 42–65) by ICR
  - The primary endpoint was met: the null hypothesis of an ORR of <25% by INV was rejected
  - Results were generally consistent with the primary analysis of MARIPOSA-2, which demonstrated an ORR of 52% (95% CI, 43–61) by INV and 64% (95% CI, 55–72) by BICR with amivantamab IV Q3W + chemotherapy[1]
  - Best confirmed overall response by INV is shown in **Figure 2A**
- Confirmed CBR was 84% (95% CI, 74–92) by INV and 83% (95% CI, 73–91) by ICR

Figure 2A: Best confirmed overall response (n=75)[a,b]



[a]Participants without a postbaseline tumor assessment were not included. [b]Confirmed ORR was 40% (95% CI, 29–52) by INV and 52% (95% CI, 40–64) by ICR.
BICR, blinded independent central review; CBR, clinical benefit rate (defined as confirmed response or stable disease for ≥11 weeks); CI, confidence interval; ICR, independent central review; INV, investigator; ORR, objective response rate; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease; SoD, sum of diameters.

1. Passaro A, et al. *Ann Oncol*. 2024;35(1):77–90.

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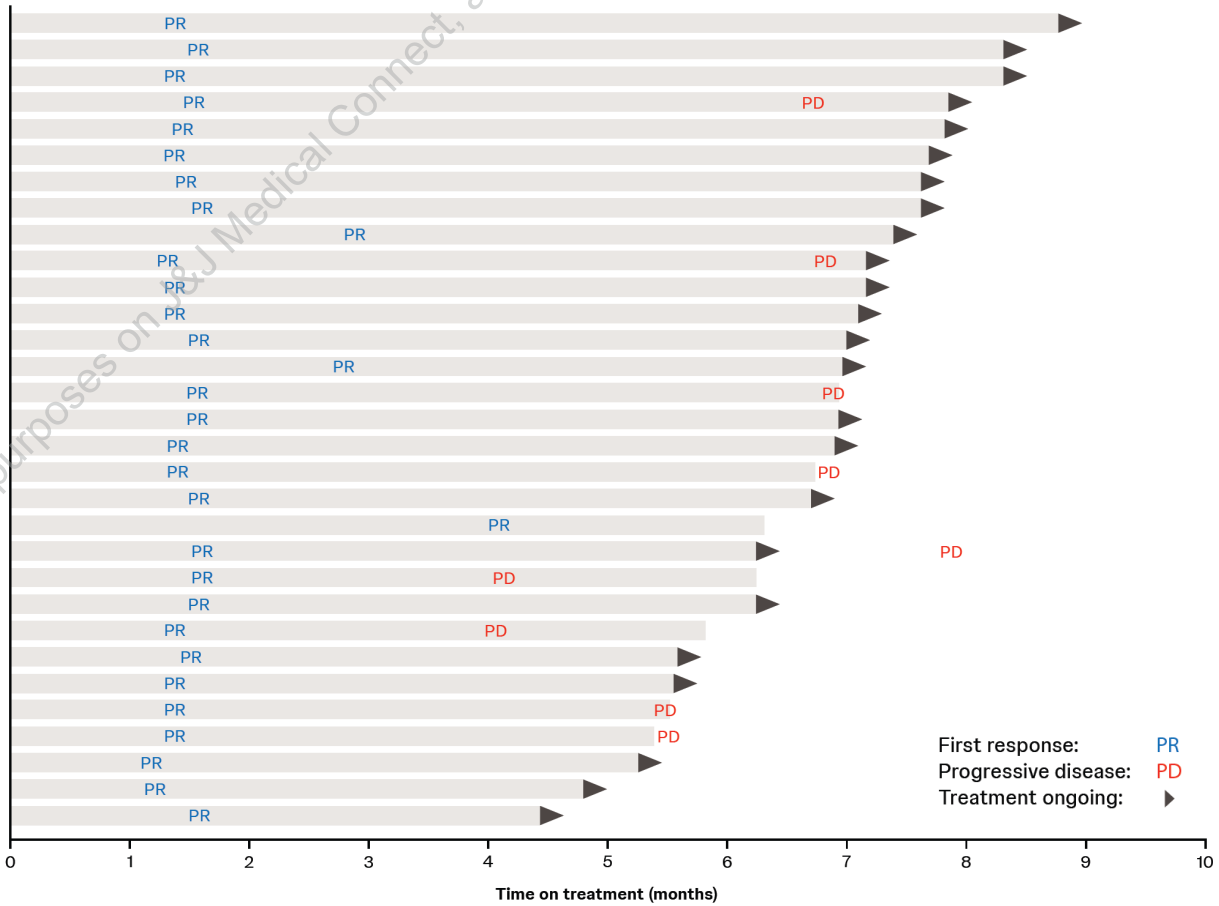
Results: Efficacy

- Among confirmed responders:
  - Median time to response was 6.6 weeks (range, 5.2–17.8)
  - Median DoR was 6.3 months (95% CI, 5.5–NE), and most responses were ongoing (71% [22/31]; **Figure 2B**)

Figure 2B: Durable and ongoing responses with amivantamab SC Q3W + chemotherapy (n=31)[a]

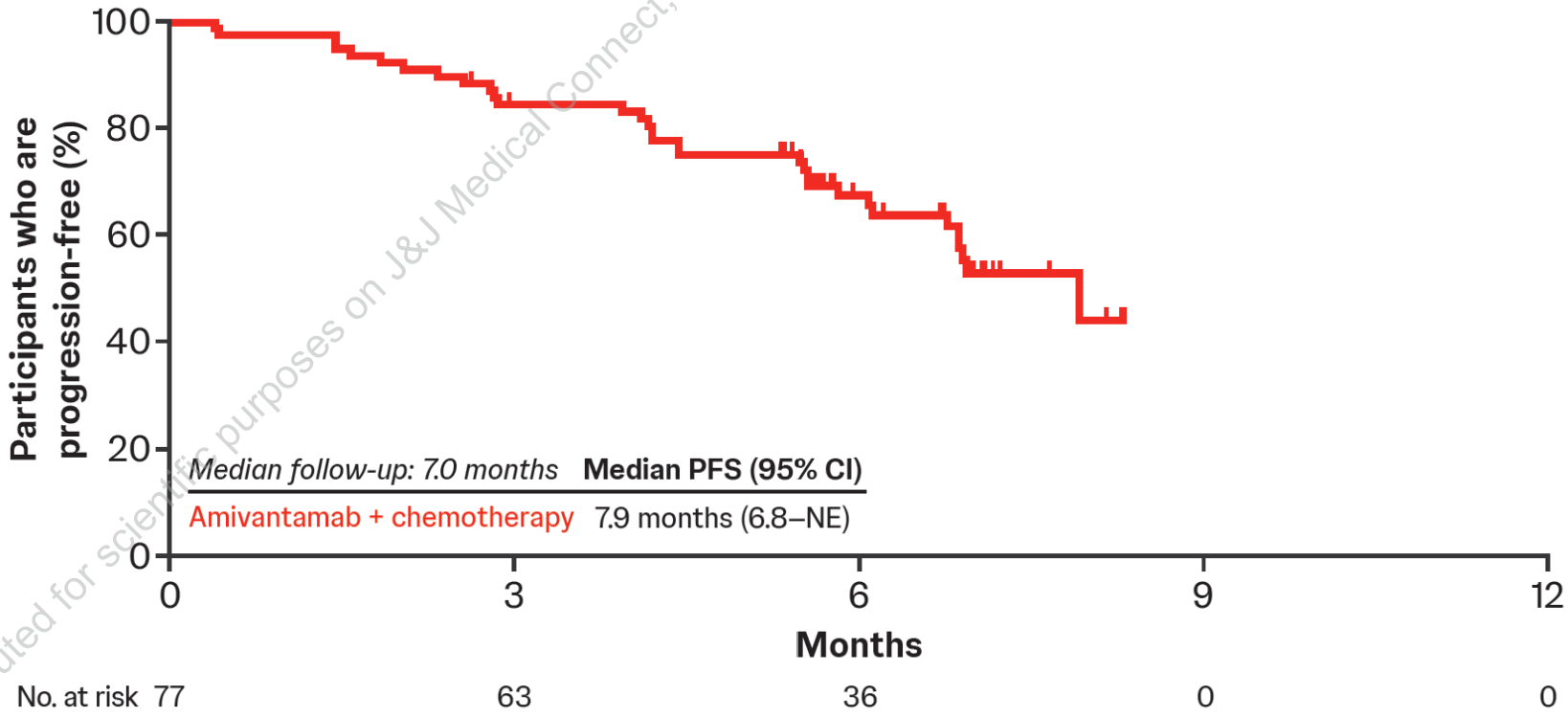


[a]In confirmed responders. Confirmation of responses by repeat assessments was performed ≥4 weeks after the criteria for PR or CR were met.
CR, complete response; DoR, duration of response; NE, not estimable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SC, subcutaneous; SD, stable disease; SoD, sum of diameters.

Results: Efficacy

- Median PFS was 7.9 months (95% CI, 6.8–NE; **Figure 3**), which was generally consistent with the primary analysis of MARIPOSA-2[1]
- Median OS was not estimable

Figure 3: PFS by INV[a]



[a]In MARIPOSA-2, INV-assessed PFS was 8.2 months (95% CI, 6.8–10.9) for amivantamab IV Q3W + chemotherapy, at a median follow-up of 8.7 months.[1]
CI, confidence interval; INV, investigator; NE, not estimable; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks.
1. Passaro A, et al. *Ann Oncol.* 2024;35(1):77–90.

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Results: Safety

- EGFR/MET-related and hematologic TEAEs were the most common, which is consistent with the known safety profile of amivantamab IV Q3W + chemotherapy,[1] and no new safety signals were identified (**Table 2**)
  - 5% of participants discontinued amivantamab due to treatment-related adverse events
- ARRs were reported in 6 (8%) participants (none grade ≥3), and all occurred and were resolved on Cycle 1 Day 1
  - Median time to ARR onset was 2.7 hours (range, 1.1–6.3) and median duration of ARR was 2.7 hours (range, 0.1–6.1)
  - The rate of ARRs was ~7-fold lower compared with amivantamab IV Q3W administration in MARIPOSA-2 (58%)[1]

Table 2: Safety profile

TEAEs (≥20%) by preferred term, n (%)	Cohort 3b (N=77)	
	All grades	Grade ≥3
Associated with EGFR inhibition		
Paronychia	42 (55)	2 (3)
Rash	39 (51)	3 (4)
Stomatitis	27 (35)	3 (4)
Dermatitis acneiform	16 (21)	2 (3)
Associated with MET inhibition		
Hypoalbuminemia	27 (35)	5 (6)
Peripheral edema	19 (25)	0
Other		
Neutropenia[a]	43 (56)	26 (34)
Nausea	35 (45)	2 (3)
Constipation	32 (42)	0
Thrombocytopenia[a]	31 (40)	10 (13)
Anemia	27 (35)	5 (6)
ALT increased	25 (33)	4 (5)
Decreased appetite	25 (33)	1 (1)
Leukopenia	24 (31)	12 (16)
Fatigue	22 (29)	4 (5)
Vomiting	20 (26)	6 (8)
AST increased	20 (26)	3 (4)
Asthenia	16 (21)	2 (3)

[a]Decreases in neutrophil and platelet counts were transient during Cycle 1 followed by recovery by Cycle 2 Day 1 and stabilization thereafter.
ALT, alanine aminotransferase; ARR, administration-related reactions; AST, aspartate aminotransferase; EGFR, epidermal growth factor receptor; IV, intravenous; Q3W, every 3 weeks; TEAE, treatment-emergent adverse events.
1. Passaro A, et al. *Ann Oncol.* 2024;35(1):77–90.

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Results: Pharmacokinetics

- Consistent with historical amivantamab IV Q3W data (mean [%CV], 359 [30] µg/mL [n=193]), amivantamab plasma concentration on Cycle 2 Day 1 was 469 (26) µg/mL (n=42)

CV, coefficient of variation; IV, intravenous; Q3W, every 3 weeks.

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Conclusions

- In PALOMA-2, participants receiving amivantamab SC Q3W + chemotherapy after disease progression on osimertinib demonstrated an ORR and PFS that were generally consistent with those who received amivantamab IV Q3W + chemotherapy in MARIPOSA-2[1]
- With the SC formulation of amivantamab, ARRs were reduced ~7-fold[1]; no new safety signals were identified
- Consistent PK profiles with historical amivantamab IV Q3W data further support the use of amivantamab SC Q3W + chemotherapy in participants with disease progression on osimertinib

ARR, administration-related reactions; IV, intravenous; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; SC, subcutaneous.

1. Passaro A, et al. *Ann Oncol.* 2024;35(1):77–90.

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Key Takeaway

In the post-osimertinib setting, the efficacy of amivantamab SC Q3W + chemotherapy is consistent with that of amivantamab IV Q3W + chemotherapy,[1] with the added tolerability and convenience benefits of an SC formulation, further supporting its use as a new SoC for patients with *EGFR*-mutated advanced NSCLC after disease progression on osimertinib

EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; SC, subcutaneous; SoC, standard of care.

1. Passaro A, et al. *Ann Oncol.* 2024;35(1):77–90.

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Acknowledgments

- We thank the individuals who participated in these studies and their families and caregivers, the physicians and nurses who cared for the participants, the staff members who supported this clinical trial, and the staff members at the study sites and involved in data collection/analyses
- This study was funded by Janssen Research & Development, LLC, a Johnson & Johnson company
- Medical writing assistance was provided by Lumanity Communications Inc. and was funded by Johnson & Johnson

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Disclosures

EN received grants or contracts from Roche, Bristol Myers Squibb, and Pfizer; received consulting fees from Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, Sanofi, Pfizer, Eli Lilly, Amgen, Johnson & Johnson, Daiichi Sankyo, Boehringer Ingelheim, AstraZeneca, Takeda, Pierre Fabre, and Qiagen; received honoraria from Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, Sanofi, Pfizer, Eli Lilly, Amgen, Johnson & Johnson, Daiichi Sankyo, Boehringer Ingelheim, AstraZeneca, Takeda, Sanofi, Pierre Fabre, Qiagen, and Bayer; received support for attending meetings and/or travel from Johnson & Johnson, Merck Sharp & Dohme, Takeda, and Roche; served on advisory boards for Roche, Apollomics, Merck Sharp & Dohme, and Transgene; and is a member of the Steering Committee of the Spanish Group of Lung Cancer (GECP). **JWN** received honoraria from BioMedical Learning Institute, Clinical Care Options, CME Matters, HMP Education, Medical Educator Consortium, Medscape, MJH Life Sciences, PeerView, Prime Oncology, Projects in Knowledge, Research to Practice, and Rockpointe CME; received consulting fees from AbbVie, Amgen, AstraZeneca, Blueprint Medicines, Calithera Biosciences, D2G Oncology, Exelixis, Genentech/Roche, Gilead, Iovance Biotherapeutics, Jounce Therapeutics, Eli Lilly, Mirati Therapeutics, Natera, Novartis, Novocure, Regeneron, Sanofi, Summit Therapeutics, Surface Oncology, Takeda, and Turning Point Therapeutics; and received institutional research funding from AbbVie, Adaptimmune, Boehringer Ingelheim, Exelixis, Genentech/Roche, GSK, Johnson & Johnson, Merck, Nektar, Novartis, and Takeda. **DS** received honoraria from AstraZeneca, Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi, Novartis, and Johnson & Johnson; received consulting fees from AstraZeneca, Merck Sharp & Dohme, Bristol Myers Squibb, Roche, Daiichi Sankyo, Johnson & Johnson, and Amgen; participated in speakers bureaus for AstraZeneca and Bristol Myers Squibb; received research funding from Merck Sharp & Dohme, AstraZeneca, Roche, Bristol Myers Squibb, Eli Lilly, and Johnson & Johnson; gave expert testimony for AstraZeneca and Bristol Myers Squibb; and received support for attending meetings and/or travel from Sanofi, Roche, AstraZeneca, and Bristol Myers Squibb. **JLT** received honoraria from Merck Sharp & Dohme, AstraZeneca, and Pfizer; and received consulting fees from Johnson & Johnson and Bristol Myers Squibb. **VCdL** received consulting fees from Roche and AstraZeneca; received honoraria from Roche, Janssen, Pfizer, Boehringer Ingelheim, Adium, AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Bristol Myers Squibb, Daiichi Sankyo, and Amgen; received support for travel from AstraZeneca, Janssen, and Daiichi Sankyo; and participated on data safety monitoring boards for Roche, Janssen, Pfizer, Boehringer Ingelheim, Adium, AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Bristol Myers Squibb, Daiichi Sankyo, and Amgen. **SB** received honoraria from Pfizer and Chugai. **MM** received consulting fees and honoraria from Johnson & Johnson. **AO** received honoraria from AstraZeneca, Chugai, ONO Pharmaceutical, Johnson & Johnson, and Indica Labs. **MR** received consulting fees from Eli Lilly, MSD Oncology, Merck Serono, Bristol Myers Squibb, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, Roche/Genentech, AbbVie, Amgen, Mirati Therapeutics, Samsung Bioepis, Sanofi/Regeneron, Daiichi Sankyo Europe GmbH, BioNTech SE, and IO Biotech; participated in speakers bureaus for Roche/Genentech, Eli Lilly, MSD Oncology, Merck Serono, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Pfizer, Novartis, Amgen, Mirati Therapeutics, and Sanofi/Aventis. **SH** received consulting fees from AstraZeneca, Bristol Myers Squibb, Roche, Sanofi, and Takeda; and received support for attending meetings and/or travel from Novartis, Merck Sharp & Dohme, and Roche. **SNW** received consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Gilead, Johnson & Johnson, and Pfizer; received institutional research funding from AbbVie, AstraZeneca, Daiichi Sankyo, Elevation Oncology, Genentech, Johnson & Johnson, Eli Lilly, Nuvalent, Inc., Ribon Therapeutics, Roche, and Xcovery. **SD, AA, MW, JM, JZ, SS,** and **MB** are employees of and may hold stock in Johnson & Johnson. **SML** received research funding from AstraZeneca, BeiGene, Bristol Myers Squibb, Boehringer Ingelheim, Bridge Biotherapeutics, Daiichi Sankyo, Gilead, GSK, JiangsuHengrui Medicine, J INTS BIO, Oscotec, Roche, Yuhan, and Johnson & Johnson; and served on advisory boards for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Johnson & Johnson, Takeda, Daiichi Sankyo, Yuhan, Guardant, Amgen, J INTS BIO, and Therapex. **K-JT** has no conflicts of interest to report.

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