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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Key Takeaway

This bridging study provided promising evidence for the efficacy and safety of subcutaneous (SC) amivantamab + lazertinib and suggested that SC amivantamab + lazertinib could be a valuable first-line treatment option for patients with epidermal growth factor receptor (*EGFR*)–mutated advanced non-small cell lung cancer (NSCLC)

Conclusions

SC amivantamab + lazertinib showed meaningful efficacy in first-line *EGFR*-mutated advanced NSCLC, with an objective response rate (ORR) comparable to that of intravenous (IV) amivantamab + lazertinib in the MARIPOSA study[1]

Overall, the safety profile of SC amivantamab + lazertinib was similar to MARIPOSA, except for administration-related reactions (ARRs; 15%, all grade 1-2) and venous thromboembolism (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 rate of VTE among patients treated with amivantamab + lazertinib

Consistent pharmacokinetic (PK) profiles further support the use of SC amivantamab + lazertinib

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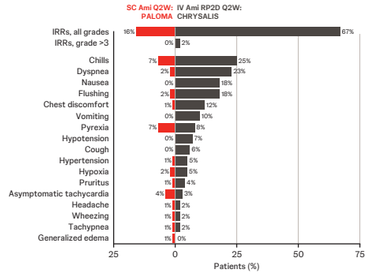
Background

- Amivantamab, an EGFR–MET bispecific antibody with immune cell–directing activity,[2–4] is approved as an IV formulation for the first- and second-line treatment of patients with *EGFR* Exon 20 insertion–mutated advanced NSCLC[5–7]
- In the MARIPOSA study, first-line amivantamab + lazertinib (a third-generation EGFR tyrosine kinase inhibitor) demonstrated superior progression-free survival versus osimertinib in patients with *EGFR* Exon 19 deletion– or L858R-mutated advanced NSCLC (23.7 vs 16.6 months, respectively; hazard ratio, 0.70; *P*<0.001)[1]
- 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 infusion-related reactions (IRRs; **Figure 1**) and short administration times (≤7 minutes for the every 2 weeks [Q2W] and every 3 weeks [Q3W] dosing regimens and 10 minutes for the every 4 weeks [Q4W] dosing regimen)[8,9]
- PALOMA-2 (ClinicalTrials.gov Identifier: NCT05498428) evaluated the efficacy, safety, and PK of first-line SC amivantamab + lazertinib in *EGFR*-mutated advanced NSCLC

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

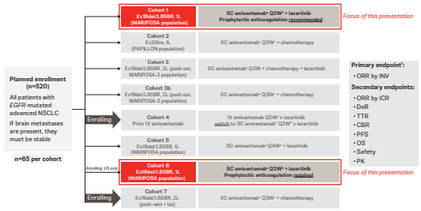


Ami, amivantamab; IRR, infusion-related reaction; IV, intravenous; Q2W, every 2 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous.

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* Exon 19 deletion– 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 Response Evaluation Criteria in Solid Tumors 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)

Figure 2: PALOMA-2 study design



*SC amivantamab was administered by manual injection in the abdomen.
[‡]SC amivantamab Q2W dose: 1600 mg (2240 mg if ≥80 kg).
[§]SC amivantamab Q3W dose: 2400 mg (3360 mg if ≥80 kg).
[¶]IV amivantamab Q2W dose: 1050 mg (1400 mg if ≥80 kg).
[#]SC amivantamab Q4W dose: 3520 mg (4640 mg if ≥80 kg).
†The primary endpoint for Cohort 4 is safety, and the secondary endpoint is patient-reported outcomes.
1L, first line; 2L, second line; ami, amivantamab; CBR, clinical benefit rate; DoR, duration of response; Ex19del, Exon 19 deletion; Ex20ins, Exon 20 insertion; ICR, independent central review; INV, investigator; IV, intravenous; laz, lazertinib; 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.

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*, epidermal growth factor receptor; Ex19del, Exon 19 deletion.

PK

- Consistent with historic IV levels (317 [32] µg/mL), mean (% coefficient of variation) 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

Efficacy

- Among all patients, the investigator-assessed ORR was 77% and the independent central review–assessed ORR was 79% (**Table 2**)
- A similar blinded independent central review–assessed ORR of 86% (95% confidence interval, 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 duration of response was not estimable

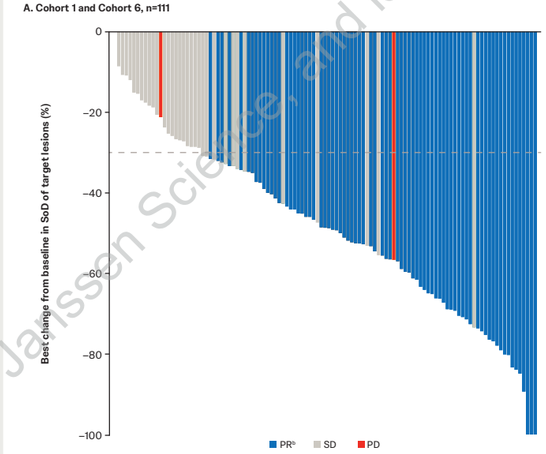
Table 2: Responses (confirmed and unconfirmed)

	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)

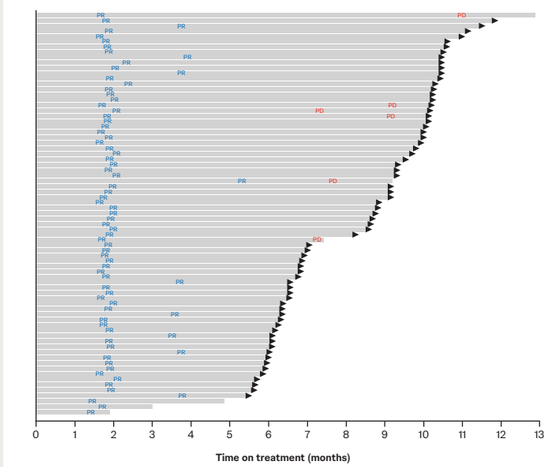
The median follow-up was 10.0 months for Cohort 1, 6.1 months for Cohort 6, and 8.6 months overall.
[a]Efficacy analyses in Cohort 6 were performed on patients who enrolled on or before July 20, 2023.
CI, confidence interval; ICR, independent central review; INV, investigator; ORR, objective response rate.

Figure 3: (A) Best response and (B) DoR in confirmed responders[a]

A. Cohort 1 and Cohort 6, n=111



B. Cohort 1 and Cohort 6, n=75



[a]Patients without a postbaseline tumor assessment were not included.
[b]Including confirmed responders only.
DoR, duration of response; INV, investigator; PD, progressive disease, PR, partial response; SD, stable disease; SoD, sum of diameters.

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,[1,10] with no new safety signals identified (**Table 3**)
  - Discontinuation of all agents due to treatment-related adverse events 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]
- A total of 71% (48/68) 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 3: Safety profile

Most common treatment-emergent AEs (≥20%), n (%)	Cohort 1 (n=68)		Cohort 6 (n=57)*		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

*One patient in Cohort 6 was enrolled but not treated at the time of the data cutoff.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EGFR, epidermal growth factor receptor; MET, mesenchymal epithelial transition.

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

	Prophylactic anticoagulation (n=105)	No prophylactic anticoagulation (n=20)	Overall (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 SMQ 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 taking 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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