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Subcutaneous Amivantamab Administered Every 4 Weeks (Q4W) in Patients With Advanced Solid Malignancies: The Phase 1b PALOMA Study

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DECLARATION OF INTERESTS

PALOMA

Natasha B. Leighl

Grants or contracts: Amgen, AstraZeneca, Eli Lily, 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: Mirati Therapeutics, Daiichi Sankyo

Background

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- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[1-3]
- IV amivantamab[a] has an IRR rate of 67% (grade ≥3: 2%)[4]
  - To manage IRRs, the first dose is split over 2 days, with an average administration time of ~4 hours
- PALOMA (NCT04606381),[b] a phase 1b study, evaluated PK and safety of SC amivantamab[4,5]
  - Q2W and Q3W SC doses have been previously reported[c]
  - SC amivantamab has an IRR rate of 16% (grade ≥3: 0%)
  - First dose does not need to be split over 2 days with an average administration time of 4–7 minutes[d]

A Q4W dose for SC amivantamab was evaluated for PK and safety

Table 1: Demographics and Baseline Characteristics

Characteristic, n (%)	SC amivantamab Q4W (n=19)
Median age, years (range)	62 (39–84)
Male/female	9 (47)/10 (53)
Body weight: <80 kg / ≥80 kg	16 (84) / 3 (16)
Race	
Asian	13 (68)
White	6 (32)
No. of prior systemic therapies	
1–3	10 (53)
≥4	9 (47)
Cancer type	
NSCLC	17 (89)
Adenocarcinoma	16 (94)
Squamous cell carcinoma	1 (6)
Other solid tumor[e]	2 (11)

[a]Q2W IV dose (1050 mg or 1400 mg if ≥80 kg); Q3W IV dose (1750 mg or 2100 mg if ≥80 kg). [b]Eligible patients were those who had advanced solid tumors and who may benefit from EGFR/MET–directed therapy. [c]The Q2W and Q3W SC amivantamab doses were identified to be 1600 mg (2240 mg if ≥80 kg) and 2400 mg (3360 mg if ≥80 kg), respectively. [d]The recommended administration rate was ~2 to 3 mL/min. [e]One patient had colorectal cancer and the other had renal cell cancer.

EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; IV, intravenous; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; 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. Minchom A, et al. Presented at: American Society of Clinical Oncology (ASCO) 2023; 2–6 June 2023; Chicago, IL, USA. 5. RYBREVANT® (amivantamab-vmjw). Published 1 April 2021. Accessed 31 January 2024. https://www.rybrevant.com.

SC Q4W Pharmacokinetics

PALOMA

- As previously reported, SC Q2W dose was 1600 mg (≥80 kg: 2240 mg) and SC Q3W dose was 2400 mg (≥80 kg: 3360 mg)[1]
- The studied Q4W dose was 3200 mg (≥80 kg: 4320 mg)[a]
  - Observed PK at Cycle 2 showed lower C_{max} as well as equal or higher C_{trough} and $AUC_{0\text{-}672h}$ versus approved IV Q2W dose
- The SC Q4W dose[b] was refined to **3520 mg (≥80 kg: 4640 mg)** to better match the steady state C_{trough} of the approved IV Q2W dose

Simulated geometric mean ratio (GMR) for 3520 mg (≥80 kg: 4640 mg) SC Q4W dose versus reference IV Q2W dose

PK parameter, GMR (90% CI)	For <80 kg: 3520 mg SC / 1050 mg IV For ≥80 kg: 4640 mg SC / 1400 mg IV	
	SC Q4W / IV Q2W	
	Cycle 2	Steady state
C_{trough} (µg/mL)	1.20 (1.12–1.30)	0.92 (0.76–1.11)
$AUC_{0\text{-}672h}$ (µg•h/mL)	1.31 (1.24–1.39)	1.27 (1.18–1.36)

- Administration time of SC amivantamab Q4W was between 7 and 10 minutes[c]
- No antidrug antibodies have been observed with SC amivantamab

[a]SC amivantamab Q4W was dosed weekly (QW) for the first 4 weeks (1600 mg [≥80 kg: 2240 mg]) and Q4W thereafter (3200 mg [≥80 kg: 4320 mg]); administration was by manual push injection in the abdomen. [b]Not exceeding 125% of the C_{max} of the approved IV dose. [c]Based on the studied dose in PALOMA and assuming an injection rate of 3 mL/min.

AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; C_{trough}, trough concentration; IV, intravenous; PK, pharmacokinetic; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous.

1. Minchom A, et al. Presented at: American Society of Clinical Oncology (ASCO) 2023; 2–6 June 2023; Chicago, IL, USA.

Safety Profile

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TEAEs (≥15%) by preferred term, n (%)	SC amivantamab Q4W (n=19)[a]	
	All grades	Grade ≥3
Associated with EGFR inhibition		
Dermatitis acneiform	14 (74)	2 (11)
Paronychia	11 (58)	1 (5)
Stomatitis	6 (32)	0
Pruritus	4 (21)	0
Associated with MET inhibition		
Peripheral edema	5 (26)	0
Hypoalbuminemia	3 (16)	0
Other		
Myalgia	8 (42)	0
Fatigue	6 (32)	0
Nausea	6 (32)	1 (5)
Back pain	5 (26)	1 (5)
Pyrexia	4 (21)	0
Vomiting	4 (21)	1 (5)
Dyspnea	4 (21)	1 (5)
Headache	4 (21)	0
IRR	3 (16)	0
Constipation	3 (16)	0
Cough	3 (16)	0
Pleural effusion	3 (16)	1 (5)
Hypomagnesemia	3 (16)	0
ALT increased	3 (16)	0

- Most common TEAEs were EGFR- and MET-related, primarily of grade 1 to 2
  - Safety profile of SC amivantamab Q4W was consistent with previous amivantamab monotherapy safety data[1]
- Grade ≥3 TEAEs with SC amivantamab occurred in 9 (47%) patients
  - 3 events were reported to be related to treatment (2 dermatitis acneiform, 1 paronychia)
- Cumulative grouped rash[b] of all grades occurred in 15 (79%) patients
- Two patients discontinued SC amivantamab, due to TEAEs both unrelated to treatment

[a]Clinical cutoff: 18 December 2023. [b]Rash is defined by the following preferred terms: dermatitis, dermatitis acneiform, rash erythematous, and rash maculopapular.

ALT, alanine aminotransferase; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous; Q4W, every 4 weeks; TEAEs, treatment-emergent adverse events.

1. Minchom A, et al. Presented at: American Society of Clinical Oncology (ASCO) 2023; 2–6 June 2023; Chicago, IL, USA.

Incidence of IRRs and IRR-related Symptoms

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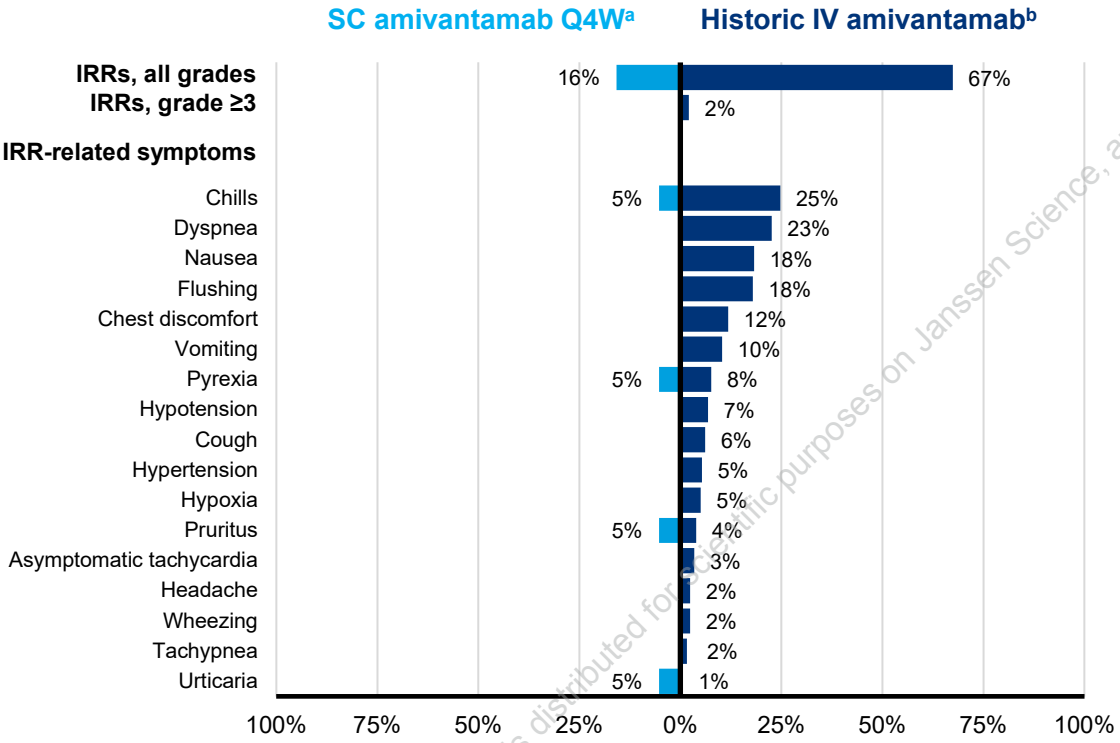

- Three patients (16%) experienced IRRs with SC amivantamab Q4W; all were grade 1 to 2
  - IRR onset was 3, 11, and >24 hours following administration
- No patients required treatment for IRRs except for one patient who received diphenhydramine and clotrimazole for pruritus
- No recurrent IRRs were reported with consecutive administrations

[a]All IRR symptoms with SC administration are listed; clinical cut off: 18 December 2023.
[b]IRR symptoms in IV amivantamab are reported in all patients treated at the RP2D in the CHRYSALIS study based on a March 2021 data cutoff.

IRR, infusion-related reaction; IV, intravenous; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; SC, subcutaneous.

Conclusions

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- The SC amivantamab Q4W dose was identified as **3520 mg (≥80 kg: 4640 mg)**[a]
- The identified SC amivantamab Q4W dose achieved comparable exposure to the approved IV dose
- Administration time of SC amivantamab Q4W was 7–10 minutes
- SC amivantamab demonstrated an IRR rate of 16%
  - IRRs were less frequent and less severe compared to historic IRRs with Q2W IV amivantamab
- SC amivantamab Q4W and Q3W dosing offers increased convenience for patients

Once monthly SC amivantamab had similar exposure, fewer IRRs, and is more convenient compared to historic IV administration

[a]SC amivantamab Q4W was dosed weekly (QW) for the first 4 weeks (1600 mg [≥80 kg: 2240 mg]) and Q4W thereafter; administration was by manual push injection in the abdomen.

IRR, infusion-related reaction; IV, intravenous; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous.

Additional Subcutaneous Amivantamab Studies

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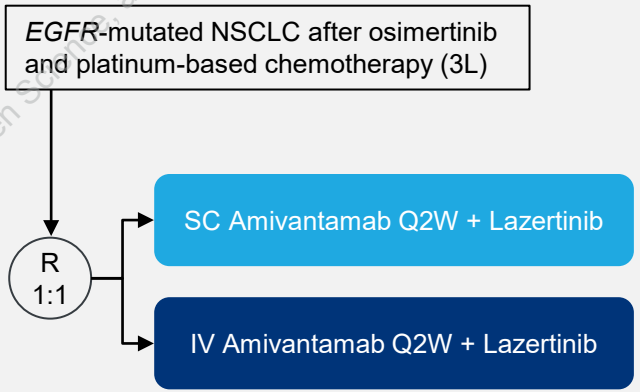
Phase 2 PALOMA-2

- SC Q2W and SC Q4W amivantamab + lazertinib in 1L *EGFR*-mutated NSCLC (**MARIPOSA** population)
- SC Q3W amivantamab + chemotherapy:
  - 1L *EGFR* Exon 20 insertion–mutated NSCLC (**PAPILLON** population)
  - *EGFR*-mutated NSCLC after progression on osimertinib (**MARIPOSA-2** population)

+ Additional cohorts

Primary endpoint: ORR per RECIST v1.1

Phase 3 PALOMA-3



Primary endpoint: PK non-inferiority[a]

[a]The co-primary PK non-inferiority endpoints were C_{trough} on Cycle 2 Day 1and AUC_{D1-D15} of SC amivantamab versus IV amivantamab.

1L, first-line; 3L, third-line; AUC, area under the curve; C_{trough}, trough concentration; D, day; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; PK, pharmacokinetic; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomized; RECIST, Response evaluation criteria in solid tumors; SC, subcutaneous.

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Acknowledgments

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- 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
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PALOMA Study Design

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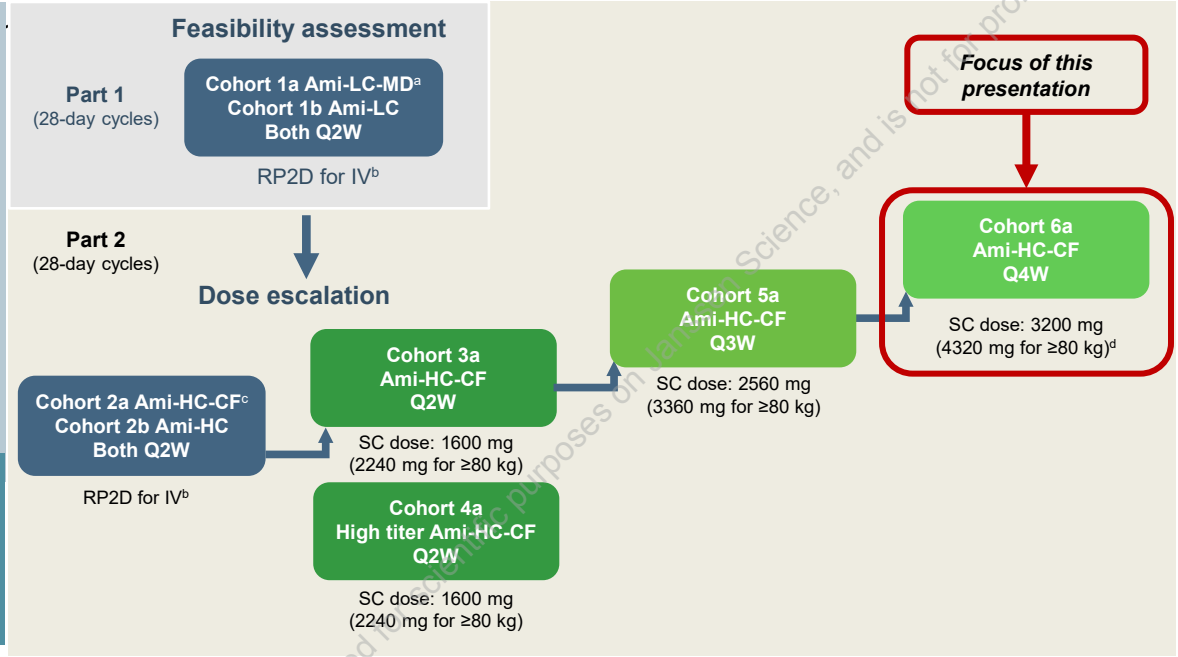
Key eligibility criteria

- Histologically or cytologically confirmed solid malignancy
- Metastatic or unresectable
- Progression from prior SOC
- May derive benefit from EGFR- or MET- directed therapy

Formulations

Ami-LC-MD: 50 mg/mL admixed with rHuPH20
Ami-LC: 50 mg/mL
Ami-HC-CF: 160 mg/mL co-formulated with rHuPH20
Ami-HC: 160 mg/mL



Primary endpoints

- C_{trough} at the end of weekly dosing (Cycle 2 Day 1)
- Safety

Secondary endpoints

- Anti-amivantamab and anti-rHuPH20 antibodies
- Soluble EGFR and MET concentrations
- ORR
- Greatest interval between dosing at steady state

[a]Mix-and-deliver: amivantamab and rHuPH20 are mixed at the hospital pharmacy before administering. [b]1050 mg (1400 mg for ≥80 kg). [c]Co-formulated: vials are ready to be administered without preparation. [d]SC dose in Cycle 1: 1600 mg (2240 mg for ≥80 kg).

Ami-HC, amivantamab high concentration; Ami-LC, amivantamab low concentration; CF, co-formulated with rHuPH20; C_{trough}, trough concentration; EGFR, epidermal growth factor receptor; MD, admixed with rHuPH20; MET, mesenchymal-epithelial transition factor; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks;
rHuPH20, recombinant human hyaluronidase (approved as an adjuvant to increase drug absorption and dispersion); RP2D, recommended phase 2 dose; SC, subcutaneous.

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