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PALOMA-2

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

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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 standard of care for patients with *EGFR*-mutated advanced NSCLC after disease progression on osimertinib

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 pharmacokinetic profiles with historical amivantamab IV Q3W data further support the use of amivantamab SC Q3W + chemotherapy in participants with disease progression on osimertinib

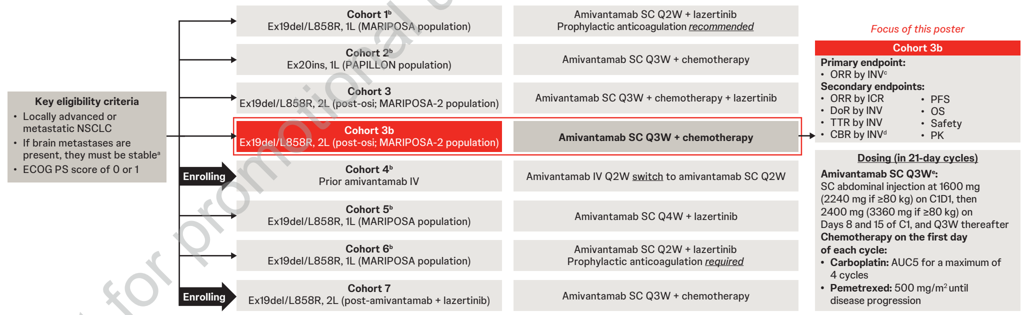
Background

- Amivantamab, an epidermal growth factor receptor (EGFR)–MET bispecific antibody with immune cell–directing activity, is approved as an intravenous (IV) formulation in combination with chemotherapy for *EGFR*-mutated advanced non-small cell lung cancer (NSCLC) after disease progression on EGFR tyrosine kinase inhibitors (TKIs)[1–6]
  - In MARIPOSA-2 (ClinicalTrials.gov Identifier: NCT04988295; median follow-up, 8.7 months), amivantamab IV every 3 weeks (Q3W) + chemotherapy demonstrated a blinded independent central review–assessed progression-free survival (PFS) of 6.3 months (95% confidence interval [CI], 5.6–8.4) and objective response rate (ORR) of 64%[1]
- In PALOMA-3 (ClinicalTrials.gov Identifier: NCT05388669), subcutaneous (SC) amivantamab every 2 weeks (Q2W) + lazertinib demonstrated noninferior pharmacokinetics and efficacy to amivantamab IV Q2W + lazertinib
  - Amivantamab SC also showed fewer infusion-related reactions (IRRs; 13% vs 66%), shorter administration time (4.8 min vs 5.0 h), higher patient convenience (85% vs 35% at the 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

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 the investigator (INV) per Response Evaluation Criteria in Solid Tumors version 1.1
- "Administration-related reaction" (ARR) was defined per the *Medical Dictionary for Regulatory Activities* preferred term (referred to as IRRs in prior IV studies)

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.[10–13] [c]Tumor response was assessed according to RECIST version 1.1. [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.

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 remained on treatment

Table 1: Baseline demographic and clinical characteristics

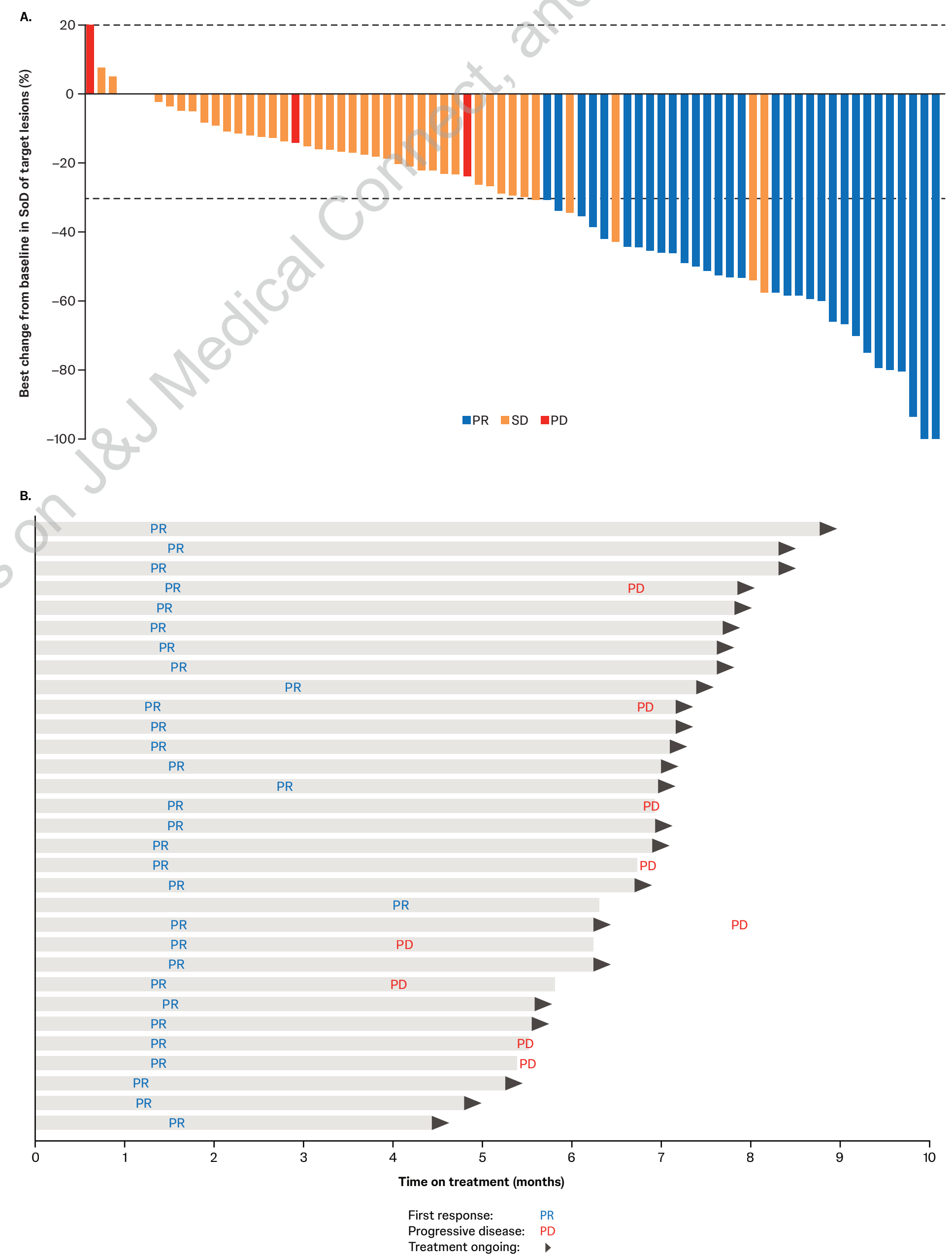
Characteristic, n (%)	Cohort 3b (N=77)
Median age (range), years	63 (41–77)
Female	44 (57)
Race	
Asian	38 (49)
White	37 (48)
Black or African American	2 (3)
ECOG PS score of 1	45 (58)
History of smoking	27 (35)
Brain metastases	27 (35)
***EGFR* mutation type**[a]	
Ex19del	44 (57)
L858R	33 (43)

[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.

Efficacy

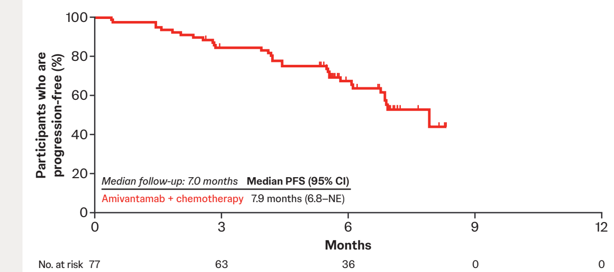
- Among all participants, ORR was 47% (95% CI, 35–59) by INV and 53% (95% CI, 42–65) by independent central review
  - The primary endpoint was met: the null hypothesis of an ORR of <25% by INV was rejected
  - Results were generally consistent with the primary analysis of MARIPOSA-2, which demonstrated an ORR of 52% (95% CI, 43–61) by INV and 64% (95% CI, 55–72) by blinded independent central review with amivantamab IV Q3W + chemotherapy[1]
  - Best confirmed overall response by INV is shown in **Figure 2A**
- Confirmed clinical benefit rate was 84% (95% CI, 74–92) by INV and 83% (95% CI, 73–91) by independent central review
- Among confirmed responders:
  - Median time to response was 6.6 weeks (range, 5.2–17.8)
  - Median duration of response was 6.3 months (95% CI, 5.5–not estimable [NE]), and most responses were ongoing (71% [22/31]; **Figure 2B**)
- 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 overall survival was not estimable

Figure 2: (A) Best confirmed overall response (n=75)[a,b] and (B) durable and ongoing responses with amivantamab SC Q3W + chemotherapy (n=31)[c]



[a]Participants without a post-baseline tumor assessment were not included. [b]Confirmed ORR was 40% (95% CI, 29–52) by INV and 52% (95% CI, 40–64) by ICR. [c]In confirmed responders. Confirmation of responses by repeat assessments was performed ≥4 weeks after the criteria for PR or complete response were met.
CI, confidence interval; DoR, duration of response; ICR, independent central review; INV, investigator; ORR, objective response rate; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SC, subcutaneous; SD, stable disease; SoD, sum of diameters.

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; PFS, progression-free survival; Q3W, every 3 weeks.

Safety

- EGFR/MET-related and hematologic treatment-emergent adverse events 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 the 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 (32)	4 (5)
Decreased appetite	25 (32)	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; AST, aspartate aminotransferase; EGFR, epidermal growth factor receptor; TEAE, treatment-emergent adverse event.

Pharmacokinetics

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

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