Amivantamab plus paclitaxel in recurrent/metastatic head & neck squamous cell cancer after disease progression on checkpoint inhibition: *Identification of the recommended combination dose from the phase 1b/2 OrigAMI-4 study*

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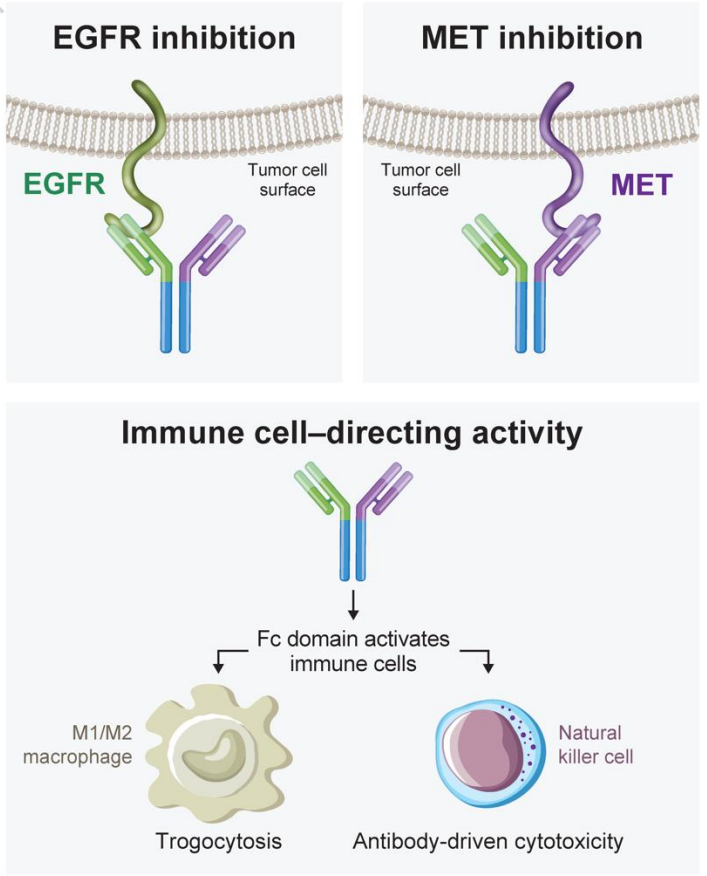
Background

- Outcomes among patients with previously treated R/M HNSCC are poor[1–4]
  - In the 2L population, paclitaxel monotherapy resulted in low response rates
- EGFR and MET overexpression occur in 80%–90% of HNSCC tumors[5,6]
- Amivantamab is an EGFR-MET bispecific antibody with a triple mechanism of action,[7,8] including (1) EGFR inhibition, (2) MET inhibition, and (3) immune cell–directing activity
- Subcutaneous amivantamab monotherapy has demonstrated rapid and durable activity in 2L+ HPV-unrelated R/M HNSCC[9]

We evaluated subcutaneous amivantamab plus paclitaxel in R/M HNSCC after disease progression on checkpoint inhibitor

Figure 1: Amivantamab's triple action mechanism



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HNSCC, head and neck squamous cell carcinoma; R/M, recurrent/metastatic.

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Methods

- OrigAMI-4 (ClinicalTrials.gov Identifier: NCT06385080) is assessing subcutaneous amivantamab in R/M HNSCC (**Figure 2**)
- Cohort 3A planned to enroll 6–12 participants to evaluate the combination dose of amivantamab and paclitaxel
  - Prior anti-EGFR and taxane therapy were exclusionary
- Primary endpoints were DLT and safety
- Responses were assessed by the investigator per RECIST v1.1

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DLT, dose-limiting toxicity; HNSCC, head and neck squamous cell carcinoma; R/M, recurrent/metastatic.

Figure 2: OrigAMI-4 study design

Eligibility Criteria

- R/M HNSCC
- No prior anti-EGFR therapy
- ECOG PS 0 or 1

For Coh 3A Initial Dose Level (DL0):

- Subcutaneous amivantamab at 2400 mg (3360 mg if ≥80 kg) was given weekly for the first 3 weeks (initial dose only: 1600 mg [2240 mg if ≥80 kg]), then Q3W (in 21-day cycles)
- Paclitaxel at 175 mg/m^2 Q3W

Cohort 1: Amivantamab monotherapy in HPV-unrelated[a]
Post-PD-(L)1 inhibitor and platinum-based chemotherapy

Cohort 2: Amivantamab plus pembrolizumab in HPV-unrelated[a]
Treatment-naïve in the recurrent/metastatic setting

Cohort 3: Amivantamab plus paclitaxel in HPV-unrelated[a]
Post-PD-(L)1 inhibitor

Cohort 4: Amivantamab monotherapy in HPV-related
Post-PD-(L)1 inhibitor and platinum-based chemotherapy

Cohort 5: Amivantamab plus pembrolizumab with carboplatin
Treatment-naïve in the recurrent/metastatic setting

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Note: All cohorts of OrigAMI-4 will utilize the subcutaneous formulation of amivantamab, which is coformulated with recombinant human hyaluronidase PH20 and manually injected in the abdomen.
[a]Participants with HPV+ oropharyngeal cancer were excluded.
ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; Q3W, every 3 weeks; R/M, recurrent/metastatic.

Results: Demographic and baseline disease characteristics

- As of 6 August 2025, 11 participants were dosed (**Table 1**), with a median follow-up of 9.8 months (range, 0.4–12.5)
- All participants had at least 1 prior line of treatment, previously receiving a checkpoint inhibitor as well as platinum-based chemotherapy

Table 1: Demographic and baseline clinical characteristics

Characteristic, n (%)	N=11
Age, median (range)	58 years (39–69)
Male / female	9 (82) / 2 (18)
Race: Asian / White / Unknown	7 (64) / 3 (27) / 1 (9)
Primary tumor location	
Hypopharynx	1 (9)
Larynx	1 (9)
Oral cavity	8 (73)
Oropharynx	1 (9)

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Results: Dose-limiting toxicity and safety

- DL0 was identified as the phase 2 combination dose
  - Among those DLT-evaluable (n=7), 1 participant experienced DLTs (grade 3 mucositis and fatigue, both resolved)
- Adverse events were mostly grade 1–2 and related to EGFR and MET inhibition (**Table 2**)
- No ARRs related to amivantamab were reported

Table 2: Safety profile

Treatment-emergent adverse events (≥20%) by preferred term, n (%)	N=11	
	All grades	Grade ≥3
Related to EGFR inhibition		
Dermatitis acneiform	5 (45)	1 (9)
Paronychia	5 (45)	0
Stomatitis	5 (45)	2 (18)
Rash	4 (36)	0
Diarrhea	3 (27)	1 (9)
Related to MET inhibition		
Hypoalbuminemia	3 (27)	0
Other		
Fatigue	5 (45)	1 (9)
Hypophosphatemia	4 (36)	0
Neutropenia	3 (27)	2 (18)
Pneumonia	3 (27)	2 (18)
Leukopenia	3 (27)	1 (9)
Myalgia	3 (27)	1 (9)
Alanine aminotransferase increased	3 (27)	0
Anemia	3 (27)	0
Back pain	3 (27)	0
Constipation	3 (27)	0
Hypokalemia	3 (27)	0
Nausea	3 (27)	0
Pyrexia	3 (27)	0

ARR, administration-related reaction; DLT, dose-limiting toxicity.

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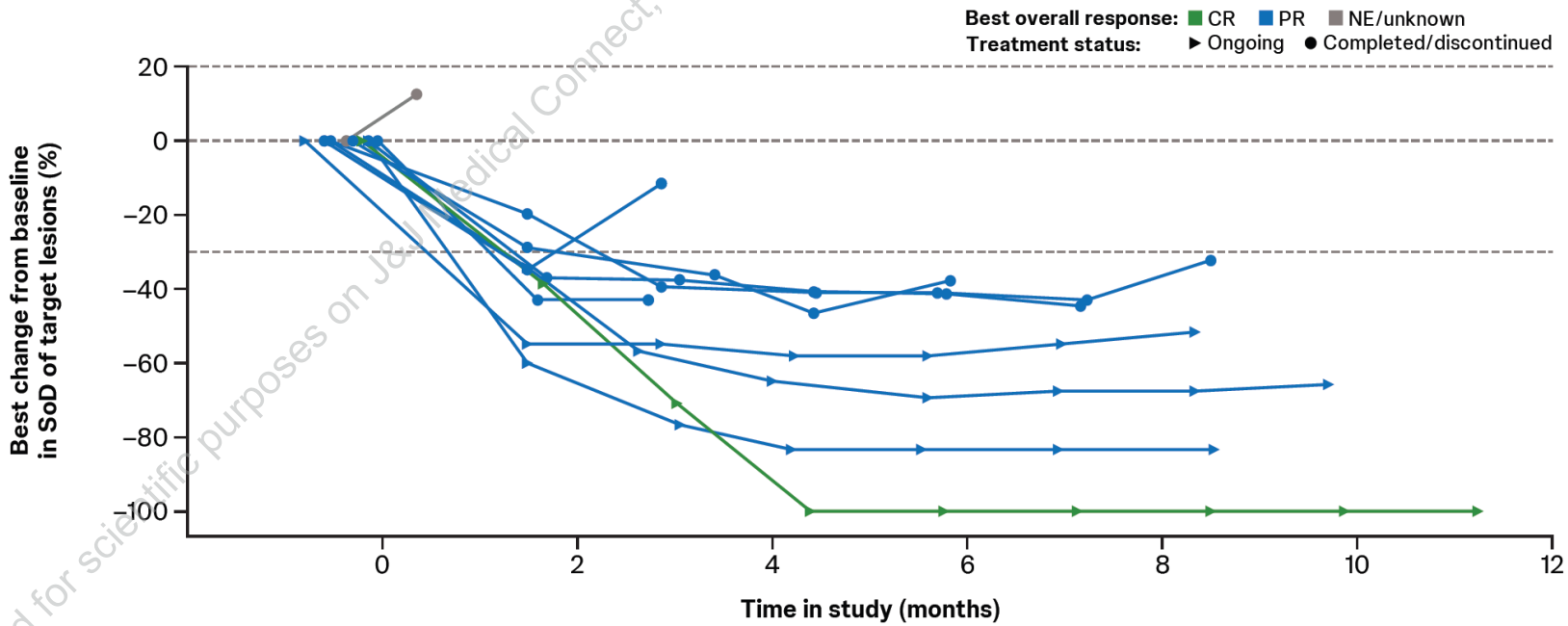
Results: Efficacy

- ORR was 64% (95% CI, 31–89)
  - As of data cutoff, median response duration was not reached
  - Among confirmed responders, 4 of 7 remained on treatment
  - 1 participant achieved a complete response and is ongoing (**Figure 3**)

Figure 3: Antitumor activity over time



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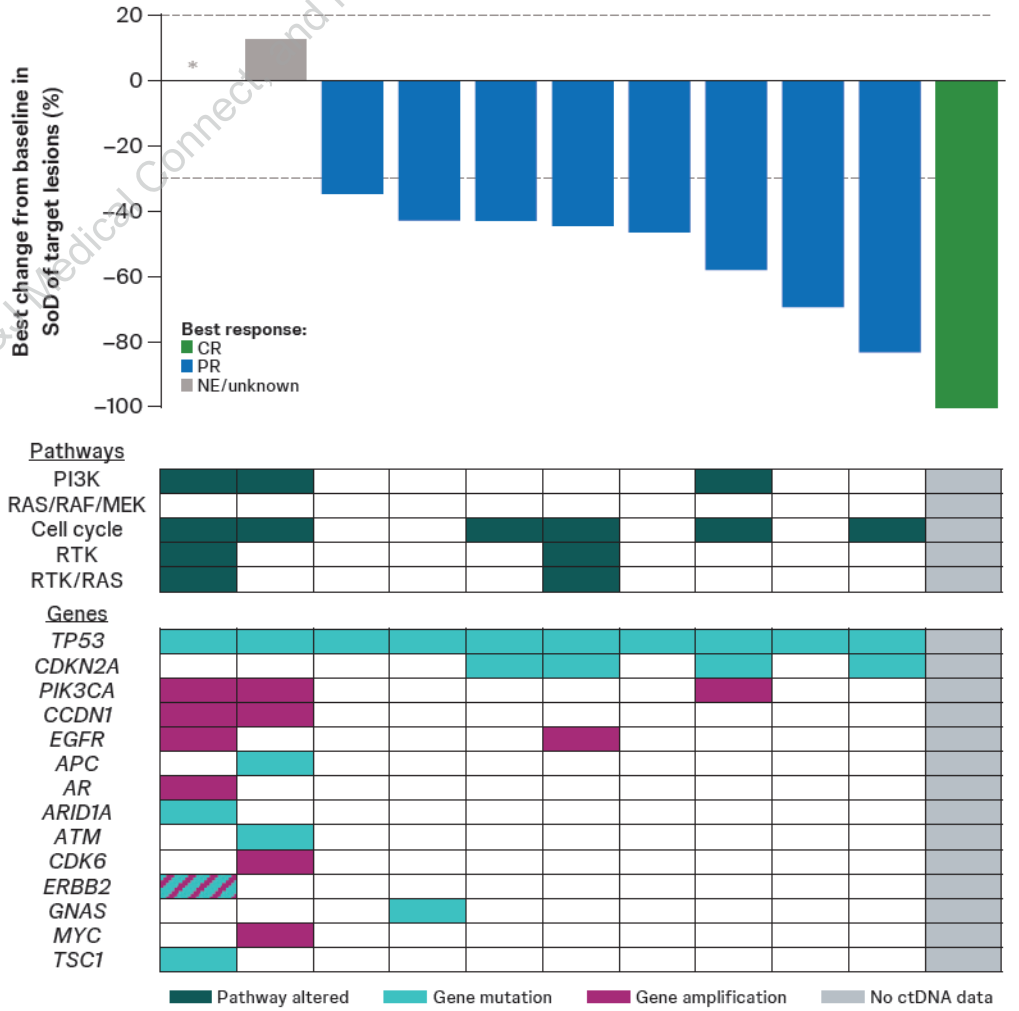
NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SoD, sum of diameters.

Results: Biomarker Analysis

- Tumor shrinkage of target lesions was seen in 9 of 11 participants
- Median time to first response was 6.6 weeks (range, 6.1–14.6)
- Median PFS and OS were not estimable
- Antitumor activity was observed regardless of baseline alterations; the 2 participants who were not evaluable had more mutations, but due to small numbers, the high response rate, and limited data on non-responders, the significance of this is unclear (**Figure 4**)

Figure 4: Best response by baseline biomarker profile



Note: Pathogenic alterations were identified by next-generation sequencing of ctDNA with Guardant360® CDx.
NE, not evaluable; SoD, sum of diameters.

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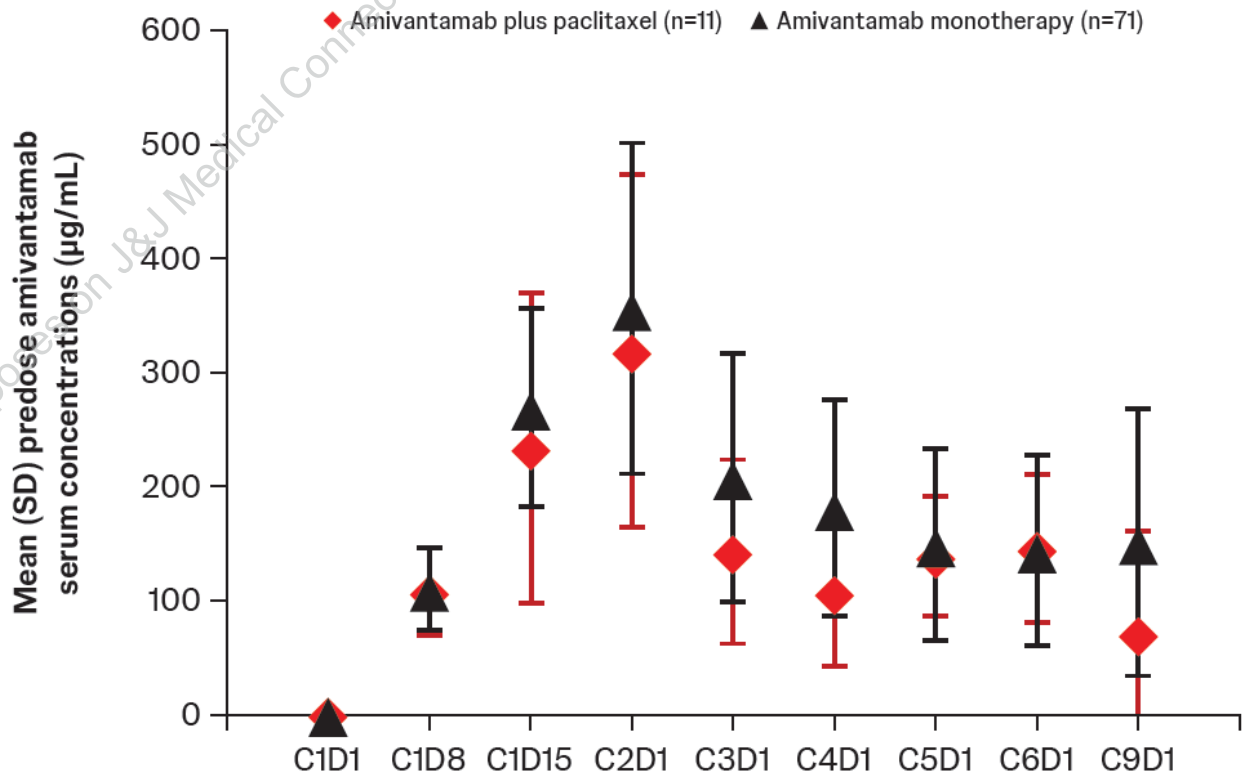
Results: Pharmacokinetics

- Predose concentrations of amivantamab were measured for a PK analysis
- Observed amivantamab serum concentrations were consistent between the amivantamab plus paclitaxel and amivantamab monotherapy cohorts, suggesting amivantamab PK exposure was not impacted by paclitaxel (**Figure 5**)

Figure 5: Observed trough amivantamab concentrations from the amivantamab plus paclitaxel and amivantamab monotherapy cohorts



PK, pharmacokinetics.

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Conclusions

- Subcutaneous amivantamab plus paclitaxel demonstrated a confirmed response in 7 of 11 (64%) participants with R/M HNSCC after disease progression on checkpoint inhibitor and platinum-based chemotherapy
- Safety profile was consistent with those of the individual agents; no ARRs related to amivantamab were reported
- Additional cohorts from OrigAMI-4 are evaluating subcutaneous amivantamab in combination with other agents, including pembrolizumab and carboplatin

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ARR, administration-related reaction; HNSCC, head and neck squamous cell carcinoma; R/M, recurrent/metastatic.

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Key Takeaway

The combination of amivantamab plus paclitaxel demonstrated durable antitumor activity among participants with 2L+ R/M HNSCC, with no new safety signals

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