# OrigAMI-5: A randomized, phase 3 study of subcutaneous amivantamab plus pembrolizumab and carboplatin vs standard of care pembrolizumab plus platinum and 5-fluorouracil as first-line treatment in recurrent/metastatic head and neck cancer

**Robert I Haddad[1], Renata Ferrarotto[2], Ye Guo[3], Kevin J Harrington[4], Lisa Licitra[5], Nabil F Saba[6], Makoto Tahara[7], Pablo Nenclares[8], Irene Braña[9], John Xie[10], Pei-Ling Chu[10], Mariah Ennis[11], Jessica Dobbs[12], Brooke Diorio[11], Priya Kim[13], Sujay Shah[13], Barbara Burtness[14]**

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Shanghai East Hospital, Shanghai, China; [4]The Institute of Cancer Research/Royal Marsden Hospital, London, UK; [5]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [6]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [7]National Cancer Center Hospital East, Kashiwa, Japan; [8]The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, London, UK; [9]Vall d' Hebron Institute of Oncology (VHIO), Barcelona, Spain; [10]Johnson & Johnson, Raritan, NJ, USA; [11]Johnson & Johnson, Titusville, NJ, USA; [12]Johnson & Johnson, Bridgewater, NJ, USA; [13]Johnson & Johnson, Spring House, PA, USA; [14]Yale School of Medicine/Yale Cancer Center, New Haven, CT, USA



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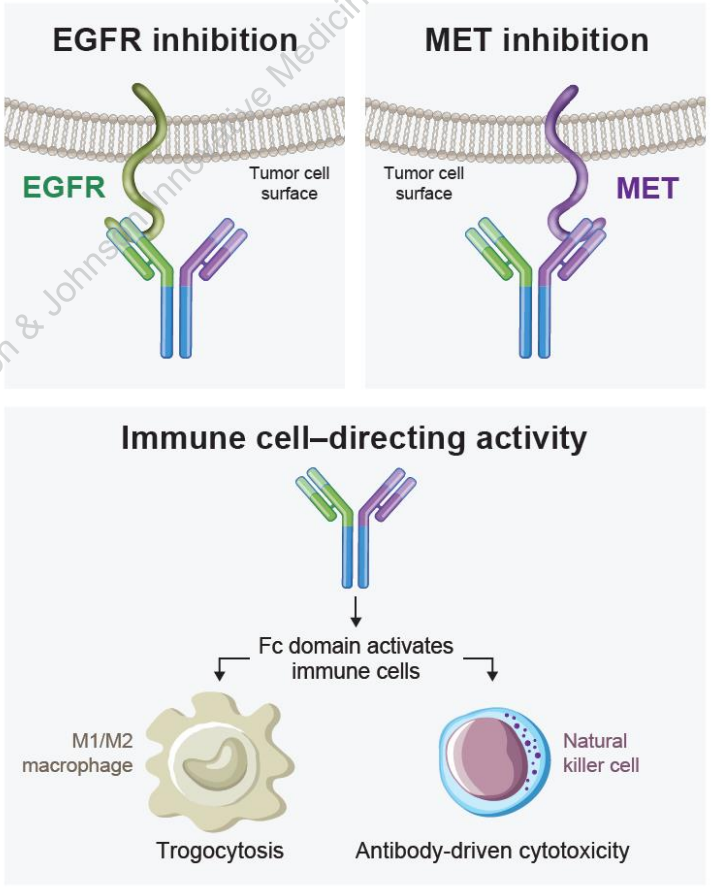
## BACKGROUND

- R/M HNSCC is associated with significant morbidity and mortality[1,2]
- Current first-line standard-of-care regimens, including combinations of pembrolizumab with or without platinum-based chemotherapy and 5-FU, yield low response rates and poor long-term outcomes, with a median survival of ~1 year[3]
- Many p16-negative HNSCC tumors exhibit EGFR and MET overexpression[4,5]
- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity (**Figure 1**)[6,7] and has demonstrated meaningful activity across several solid tumor types[8–10]
- In prior reports of the phase 1b/2 OrigAMI-4 study (NCT06385080):
  - Subcutaneous amivantamab monotherapy demonstrated a confirmed investigator-assessed ORR of 47% in R/M HNSCC after immune checkpoint inhibitor and platinum-based chemotherapy[8]
  - Among previously untreated R/M HNSCC, subcutaneous amivantamab plus pembrolizumab demonstrated a confirmed ORR of 56%[11]

**Figure 1: Amivantamab's MoA[12]**




5-FU, 5-fluorouracil; EGFR, epidermal growth factor receptor; MoA, mechanism of action; ORR, objective response rate; R/M HNSCC, recurrent and/or metastatic head and neck squamous cell cancer.





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## OBJECTIVE

This global, randomized, phase 3 study is evaluating the efficacy and safety of subcutaneous amivantamab in addition to pembrolizumab and carboplatin, as compared with the standard of care (pembrolizumab plus carboplatin or cisplatin and 5-FU), as first-line therapy for participants with R/M HNSCC

5-FU, 5-fluorouracil; R/M HNSCC, recurrent and/or metastatic head and neck squamous cell cancer.





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## METHODS

- OrigAMI-5 is a randomized, open-label, phase 3 study currently recruiting participants with R/M HNSCC (**Figure 2**)
  - Primary tumor locations of oral cavity, hypopharynx, larynx and HPV-negative oropharyngeal cancer are eligible
  - HPV-positive oropharyngeal cancer and any known HPV positivity are excluded
- Participants will be randomized 1:1 to receive subcutaneous amivantamab with pembrolizumab and carboplatin, or 5-FU plus pembrolizumab and investigator's choice of carboplatin or cisplatin

5-FU, 5-fluorouracil; HPV, human papillomavirus; R/M HNSCC, recurrent and/or metastatic head and neck squamous cell cancer.





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## METHODS

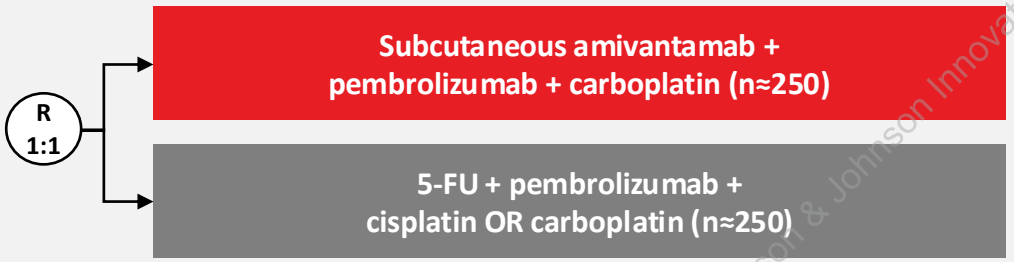
### Figure 2: OrigAMI-5 study design

**Key eligibility criteria**

- R/M HNSCC
- No prior anti-EGFR therapy
- ECOG PS score of 0 or 1
- Primary tumor locations of oral cavity, hypopharynx, larynx, or HPV-negative oropharyngeal cancer

**Stratification factors**

- PD-L1 CPS: <1 vs 1–19 vs ≥20
- ECOG PS: 0 vs 1




**Dosing schedule (in 21-day cycles):**

- **Subcutaneous amivantamab**[a] at 2400 mg (3360 mg if ≥80 kg) weekly for the first cycle (initial dose only: 1600 mg or 2240 mg if ≥80 kg), then Q3W for up to 24 months
- **Pembrolizumab** at 200 mg IV Q3W for up to 24 months
- **Carboplatin** at AUC 5 mg/mL·min IV Q3W for up to 6 cycles
- **Cisplatin** at 100 mg/m$^2$ IV Q3W for up to 6 cycles
- **5-FU** at 1000 mg/m$^2$/day continuous IV infusion on Days 1 to 4 of each cycle for up to 6 cycles

**Primary endpoints:**

- Objective response rate by BICR per RECIST v1.1
- Overall survival[b]

**Secondary endpoints:**

- Progression-free survival by BICR per RECIST v1.1
- Duration of response by BICR
- Patient-reported outcomes
- Incidence and severity of adverse events and laboratory abnormalities

[a]Coformulated with recombinant human hyaluronidase PH20 (rHuPH20). [b]For the European Union and any applicable country/region, the primary endpoint is overall survival only.

5-FU, 5-fluorouracil; AUC, area under the curve; BICR, blinded independent central review; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell cancer; HPV, human papillomavirus; IV, intravenous; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; R, randomized; R/M, recurrent/metastatic; RECIST v1.1, Response Evaluation Criteria in Solid Tumors v1.1.



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## METHODS

- Key inclusion and exclusion criteria are shown in **Table 1**

### Table 1: Key inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Histologically or cytologically confirmed R/M HNSCC<br>• Primary sites limited to oral cavity, hypopharynx, larynx, and HPV-negative oropharyngeal cancer<br>• No prior systemic therapy for R/M disease; prior curative-intent therapy allowed if completed >6 months prior without early progression<br>• ECOG PS score of 0 or 1<br>• PD-L1 CPS determined locally using validated testing within 6 months prior (for stratification; positivity not required for enrollment) | • Any prior anti-EGFR or anti-MET therapy in any setting<br>• Any known HPV positivity<br>• Untreated brain metastases or leptomeningeal disease; treated brain metastases allowed only if clinically stable and off steroids (≤10 mg prednisone or equivalent)<br>• Current or prior ILD, pneumonitis, or pulmonary fibrosis<br>• Uncontrolled illness, including (not limited to) ongoing or active infection |

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell cancer; HPV, human papillomavirus; ILD, interstitial lung disease; PD-L1, programmed death ligand 1; R/M, recurrent/metastatic.





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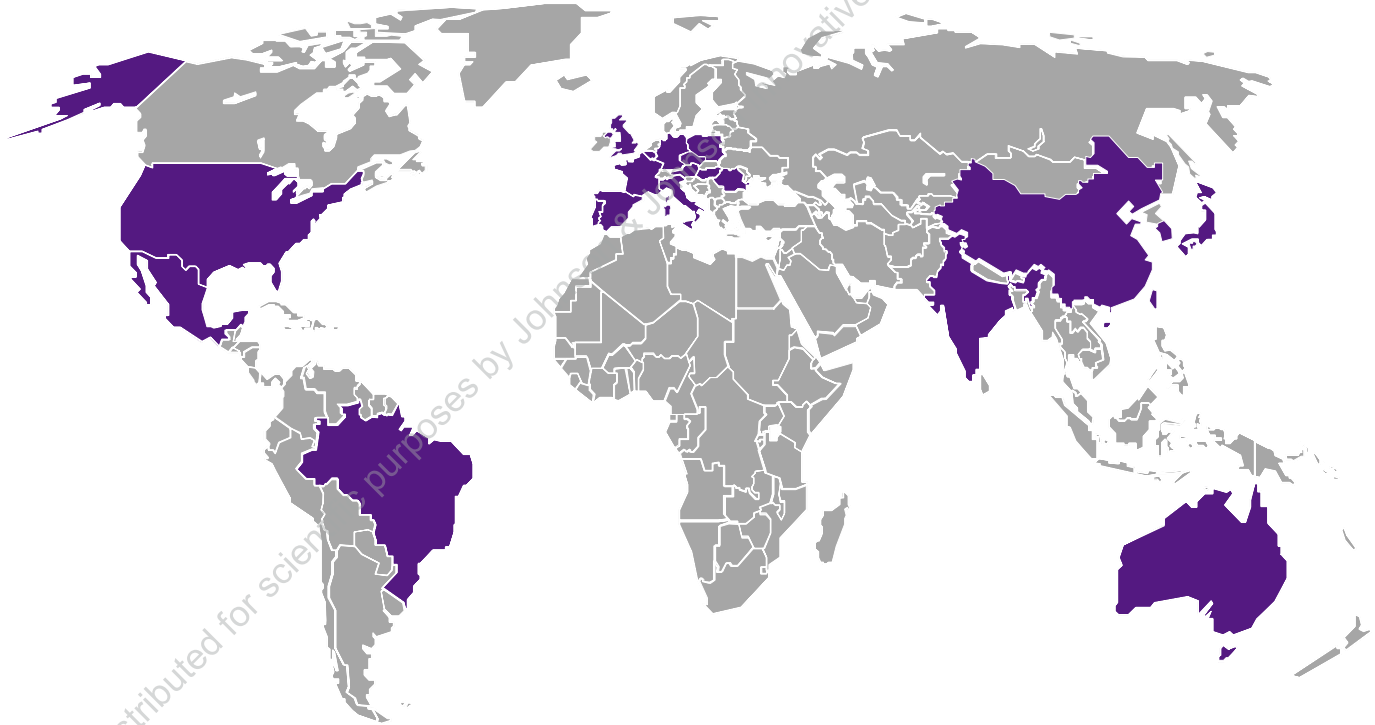
## METHODS

- The multicenter, global OrigAMI-5 study is planned to open at approximately 205 sites across 22 countries (**Figure 3**)

**Figure 3: Participating countries**







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## SUMMARY

OrigAMI-5 is a global, randomized, phase 3 study evaluating amivantamab plus pembrolizumab and carboplatin versus standard of care (pembrolizumab plus carboplatin or cisplatin and 5-FU) as first-line therapy for participants with R/M HNSCC

5-FU, 5-fluorouracil; R/M HNSCC, recurrent and/or metastatic head and neck squamous cell cancer.





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## CURRENT STATUS AND REGISTRATION INFORMATION

### Current status:

OrigAMI-5 is currently enrolling, with a goal of approximately 500 participants

### Registration information:

This study is registered with ClinicalTrials.gov (Identifier: NCT07276399)



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## DISCLOSURES:

**RIH** received research funding to the institution from Merck, Bristol Myers Squibb, AstraZeneca, Genentech, Pfizer, Kura Oncology, EMD Serono, Incyte, Merus, AVEO, and GSK; received honoraria/consulting or advisory fees from Merck, Eisai, AstraZeneca, GSK, EMD Serono, Bayer, Boehringer Ingelheim, ALX Oncology, AVEO, Genmab, PDS Biotechnology, Scholar Rock, Genzyme, Johnson & Johnson, RAPT Therapeutics, AbbVie, Astellas Pharma, and Bristol Myers Squibb/Celgene; reports patents, royalties, or other intellectual property with UpToDate; reports other relationships with Nanobiotix, ISA Pharmaceuticals, Boehringer Ingelheim, Hookipa Pharma, and Incyte; holds stock/other ownership interests in Tosk Inc.; and has a leadership role with the National Comprehensive Cancer Network (NCCN).

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