TPS3636 **Poster Session**

OrigAMI-2: A randomized, phase 3 study of amivantamab vs cetuximab, both in combination with FOLFOX or FOLFIRI, as first-line treatment in left-sided *RAS/BRAF* wild-type metastatic colorectal cancer.

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Background: Approximately 50% of patients diagnosed with metastatic colorectal cancer (mCRC) are wild-type for *KRAS*, *NRAS*, and *BRAF* (*RAS/BRAF* WT). Standard initial therapy for left-sided *RAS/BRAF* WT mCRC is doublet chemotherapy (FOLFOX or FOLFIRI) combined with anti-EGFR therapy. However, resistance is nearly inevitable. *MET* alterations are known resistance mechanisms to EGFR inhibition, with *MET* amplification occurring in 5%-23% of EGFR-resistant mCRC. Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity that is approved by the FDA for 4 indications in *EGFR*-mutated advanced non-small cell lung cancer. In the phase 1b/2 OrigAMI-1 study (NCT05379595), the combination of amivantamab plus FOLFOX or FOLFIRI demonstrated rapid and durable antitumor activity, regardless of tumor sidedness, in participants with *RAS/BRAF* WT mCRC (Pietrantonio ESMO 2024). The objective of this phase 3 randomized study is to assess the efficacy of amivantamab, as compared with cetuximab, both in combination with FOLFOX or FOLFIRI, as first-line therapy for participants with left-sided *RAS/BRAF* WT unresectable or metastatic CRC. **Methods:** The multicenter, global OrigAMI-2 study (NCT06662786) is planned to open in 216 sites in 21 countries. Eligible participants will be WT for *KRAS*, *NRAS*, and *BRAF* by local testing, have left-sided unresectable or metastatic colorectal cancer, and be treatment-naïve for advanced disease. Left-sided disease will be defined as a primary tumor arising from the splenic flexure, descending colon, sigmoid colon, rectosigmoid, or rectum. Key exclusion criteria include known dMMR/MSI-H status, HER2-positive or amplified tumor, and prior exposure to EGFR or MET targeting agents. Approximately 1000 participants will be randomly assigned 1:1 to receive subcutaneous amivantamab (co-formulated with recombinant human hyaluronidase [rHuPH20]) or intravenous cetuximab, both combined with FOLFOX or FOLFIRI (investigator's choice). Randomization will be stratified by chemotherapy choice (FOLFOX or FOLFIRI), limited disease (yes or no), and prior adjuvant therapy (yes or no). The primary endpoint will be progression-free survival by blinded independent central review. Secondary endpoints include overall survival, objective response rate, duration of response, and patient-reported outcomes. Safety assessments will include monitoring adverse events and laboratory abnormalities. Clinical trial information: NCT06662786. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson Company.