TPS3638 Poster Session

OrigAMI-3: A randomized, phase 3 study of amivantamab plus FOLFIRI vs cetuximab or bevacizumab plus FOLFIRI in participants with recurrent, unresectable, or metastatic *RAS/BRAF* wild-type colorectal cancer.

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Background: Among patients with metastatic colorectal cancer (mCRC), approximately 50% are wild-type for *KRAS*, *NRAS*, and *BRAF* (*RAS/BRAF* WT) without actionable genomic alterations. Standard first-line therapy for *RAS/BRAF* WT mCRC is 5-FU-based doublet chemotherapy (FOLFOX or FOLFIRI) plus anti-EGFR or anti-VEGF therapy. The choice of second-line treatment is dependent on first-line treatment (eg, oxaliplatin-based chemotherapy in the first-line necessitates irinotecan-based in the second-line, and vice versa). Known resistance mechanisms to anti-EGFR therapy are *MET* alterations, with *MET* amplification occurring in 5%-23% of EGFR-resistant mCRC and increasing in prevalence over subsequent lines of therapy. Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity and is FDA-approved for 4 indications in *EGFR*-mutated advanced non-small cell lung cancer. In the phase 1b/2 OrigAMI-1 study (NCT05379595), amivantamab plus FOLFIRI demonstrated promising antitumor activity, independent of line of therapy, in participants (pts) with *RAS*/*BRAF* WT mCRC without prior anti-EGFR exposure (Pietrantonio ESMO 2024). The objective of this phase 3 randomized study is to assess the efficacy of amivantamab plus FOLFIRI vs cetuximab or bevacizumab plus FOLFIRI, as second-line therapy for pts with recurrent *RAS*/*BRAF* WT mCRC. **Methods:** The global OrigAMI-3 study (NCT06750094) is planned to open in 230 sites in 25 countries. Eligible pts will be WT for *KRAS*, *NRAS*, and *BRAF*, have recurrent unresectable or mCRC, and must have had disease progression on one prior line of systemic therapy for metastatic disease (prior regimen must be fluoropyrimidine-based and oxaliplatin-based therapy). Pts with treated, stable, and asymptomatic brain metastases are allowed. Key exclusion criteria include known dMMR/MSI-H status without prior immunotherapy, HER2-positive or amplified tumor, and prior exposure to irinotecan or agents targeting EGFR or MET. Approximately 700 pts will be randomly assigned 1:1 to receive subcutaneous amivantamab (co-formulated with recombinant human hyaluronidase [rHuPH20]) plus FOLFIRI vs intravenous cetuximab or bevacizumab (investigator's choice, per local guidelines) plus FOLFIRI. Randomization will be stratified by choice of cetuximab or bevacizumab, primary tumor location (left vs right-sided), duration of first-line therapy (< 6 months or ≥ 6 months), and prior anti-VEGF therapy (yes or no). The dual primary endpoints will be progression-free survival by blinded independent central review and overall survival. Secondary endpoints include objective response rate, duration of response, and patient-reported outcomes. Safety assessments will include monitoring adverse events and laboratory abnormalities. Clinical trial information: NCT06750094. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.