

MOUNTAINEER-03: Phase 3 study of tucatinib, trastuzumab, and mFOLFOX6 as first-line treatment in HER2+ metastatic colorectal cancer—Trial in progress.

Tanios S. Bekaii-Saab, Eric Van Cutsem, Josep Tabernero, Salvatore Siena, Takayuki Yoshino, Yoshiaki Nakamura, Kanwal Pratap Singh Raghav, Andrea Cercek, Volker Heinemann, David E. Adelberg, James Edward Ward, Shan Yang, Thierry Andre, John H Strickler

Mayo Clinic, Scottsdale, AZ; University Hospital Gasthuisberg and University of Leuven, Leuven, Belgium; Vall D'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; Grande Ospedale Metropolitano Niguarda and Università degli Studi di Milano, Milan, Italy; National Cancer Center Hospital Japan East, Kashiwa, Japan; MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center, New York, NY; University of Munich, Munich, Germany; Merck & Co., Inc., Kenilworth, NJ; Seagen, Inc., Bothell, WA; Seagen Inc., Bothell, WA; Sorbonne Université et INSERM 'Instabilité des Microsatellites et Cancer, Hôpital Saint Antoine, Paris, France; Duke University Medical Center, Durham, NC

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Background: Current standard of care (SOC) for treatment (tx) of metastatic colorectal cancer (mCRC) is multi-agent chemotherapy, w/ or w/o a VEGF- or EGFR-inhibitor. HER2 is a validated clinical target in breast and gastric cancers. HER2 amplification occurs in 3%-5% of patients (pts) w/ mCRC; the rate of HER2 amplification can increase to ~10% in pts w/ RAS/BRAF wild-type mCRC tumors. Tucatinib (TUC), a highly selective, HER2-directed tyrosine kinase inhibitor, is approved in multiple regions for HER2+ metastatic breast cancer and is being investigated in gastrointestinal cancers. MOUNTAINEER (NCT03043313) evaluated the safety and efficacy of TUC and trastuzumab (Tras) in pts w/ tx refractory RAS wild-type, HER2+ mCRC. Results from the primary endpoint analysis showed clinically meaningful activity (confirmed ORR of 38.1% and median DOR of 12.4 months) and demonstrated TUC + Tras was well tolerated with a low discontinuation rate (5.8%) and no deaths due to AEs. MOUNTAINEER-03 will further investigate TUC in combo w/ mFOLFOX and Tras in pts w/ RAS wild-type, HER2+ mCRC.

Methods: MOUNTAINEER-03 (NCT05253651) is a global, open label, randomized, phase 3 study for 1L tx of HER2+ and RAS wild-type mCRC. Approximately 400 pts will be randomized 1:1 to the TUC experimental arm (TUC [300 mg PO BID] + Tras + mFOLFOX) or the SOC arm (mFOLFOX alone or in combo w/ either bevacizumab or cetuximab). HER2 status is determined centrally w/ tissue based HER2 immunohistochemistry and in situ hybridization assays. Eligible pts must not have received prior tx in the metastatic setting but may have received adjuvant tx if completed > 6 months prior to enrollment. Pts must be ≥18 years of age w/ an ECOG performance status of ≤1 and RAS wild-type mCRC. Pts w/ treated stable central nervous system metastases are eligible. Randomization is stratified by primary tumor location (left-sided vs other) and liver metastases (presence/absence). Primary endpoint is progression-free survival per RECIST v1.1, assessed by blinded independent central review (BICR). Key secondary endpoints are overall survival and confirmed objective response rate per RECIST v1.1 assessed by BICR. Enrollment is ongoing in the US, w/ global sites planned.