FPN 438TiP

MOUNTAINEER-03: PHASE 3 STUDY OF TUCATINIB, TRASTUZUMAB, AND MODIFIED FOLFOX6 AS FIRST-LINE TREATMENT IN HER2+ METASTATIC COLORECTAL CANCER (TRIAL IN PROGRESS)

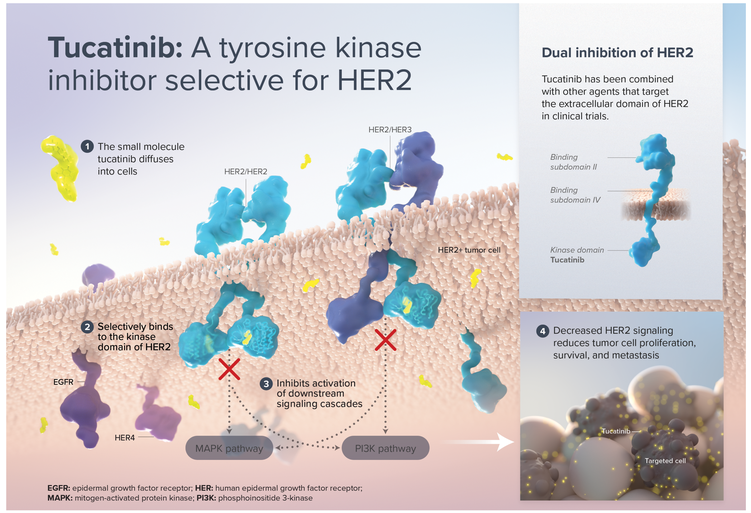
Thierry Andre[1], Tanios Bekaii-Saab[2], Josep Tabernero[3], Salvatore Siena[4], Takayuki Yoshino[5], David Adelberg[6], James Ward[7], Shan Yang[7], John Strickler[8], Eric Van Cutsem[9]

[1]Sorbonne Université et INSERM 'Instabilité des Microsatellites et Cancer, Hôpital Saint Antoine, Paris, France; [2]Mayo Clinic, Scottsdale, AZ, USA; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]Università degli Studi di Milano and Grande Ospedale Metropolitano Niguarda, Milan, Italy; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Merck & Co., Inc., Rahway, NJ, USA; [7]Seagen Inc., Bothell, WA, USA; [8]Duke University Medical Center, Durham, NC, USA; [9]University Hospital Gasthuisberg-University of Leuven, Leuven, Belgium

Background and Rationale

- Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death worldwide[1]
- Approximately 20% of patients have metastatic disease at the time of diagnosis, and up to 40% of patients initially diagnosed with locoregional cancer will develop recurrent disease[2,3]
- Current standard of care for treatment of metastatic colorectal cancer (mCRC) is multi-agent chemotherapy, with or without a VEGF- or EGFR-inhibitor; treatments are not curative and survival outcomes remain poor[4,5]
- HER2 amplification is present in approximately 3%–5% of patients with mCRC and approximately 5%–14% of patients with RAS/BRAF WT mCRC[6–10]
- HER2 alterations have been identified as potential mechanisms of primary resistance and poor response to anti-EGFR therapies[9,11–14]
  - Recent developments have increased interest in HER2 as a therapeutic target for mCRC and HER2-directed therapies as a mechanism to better tailor treatment for some patients
  - There are currently no FDA- or EMA-approved therapies for HER2+ mCR
- Tucatinib is a highly selective HER2-directed TKI
  - Preclinical data across tumor types, including CRC, show strong evidence supporting the increased activity of tucatinib in combination with trastuzumab relative to other agents
    - » Tumor regression rates in tucatinib and trastuzumab monotherapy were 26% and 15%, respectively; tumor regression rates were 66% when tucatinib and trastuzumab were administered in combination[15]
  - Tucatinib is currently approved in multiple regions for patients with HER2+ metastatic breast cancer who have received one or more prior anti-HER2 therapies in the metastatic setting[16]
  - Tucatinib is currently being investigated in gastrointestinal cancers
  - Results from the primary endpoint analysis from the single-arm phase 2 MOUNTAINEER trial (NCT03043313) showed durable and clinically meaningful antitumor activity of tucatinib and trastuzumab in patients with previously treated RAS wild-type, HER2+ mCRC
    - » cORR of 38.1%, median DOR per BICR of 12.4 months[17]
      - ▫ Median duration of follow-up of 16.3 months
    - » Tucatinib plus trastuzumab was well tolerated with a low discontinuation rate (5.8%) and no deaths due to AEs
      - ▫ Most common AE was diarrhoea, which was predominately low grade (Grade 3 events, 3.5% and no Grade 4 events)

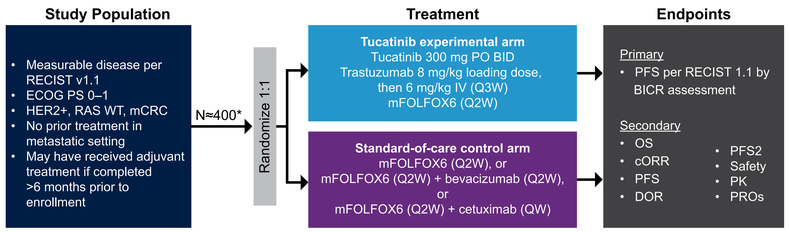
Tucatinib Proposed Mechanism of Action



Tucatinib is an investigational agent, and its safety and efficacy have not been established. There is no guarantee that tucatinib will receive regulatory approval and become commercially available for uses being investigated.

Study Design

- MOUNTAINEER-03 (NCT05253651) is a global, open-label, randomized, phase 3 study of tucatinib with trastuzumab and mFOLFOX6 versus standard of care for the first-line treatment of HER2+ and RAS wild-type mCRC



*Stratification by both primary tumor location (left-sided versus all other) and liver metastases (presence or absence)

Eligibility

Key Inclusion Criteria

- Histologically and/or cytologically documented adenocarcinoma of the colon or rectum, which is metastatic and/or unresectable
- HER2+ disease, determined centrally using a tissue-based HER2 assay
- *RAS* wild-type mCRC, determined locally or centrally
- ≥18 years
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1
- Life expectancy of ≥3 months
- Adequate baseline hematologic, hepatic, renal, coagulation, and cardiac function
- Based on MRI or CT with contrast, previously treated, asymptomatic brain metastases permitted

Key Exclusion Criteria

- Received prior treatment in the metastatic setting or completed adjuvant treatment ≤6 months prior to enrollment
- Received radiation therapy within 14 days prior to enrollment (or within 7 days of stereotactic radiosurgery)
- Previous treatment with anti-HER2 therapy
- Clinically significant cardiopulmonary disease
- Ongoing ≥Grade 2 diarrhea of any etiology at screening

Key Study Assessments

Efficacy

- Radiological disease assessments (CT and/or MRI) will be performed at baseline, during study treatment (every 6 weeks ±7 days for the first 72 weeks then every 12 weeks ±7 days), and at the end of treatment visit

Pharmacokinetics

- Plasma concentrations of tucatinib (blood samples collected on Day 1 of Cycles 2 to 6)
- Pharmacodynamic and Biomarker Assessments

Safety

- Laboratory Assessments will be performed locally

Patient-reported Outcomes

- The EORTC QLQ-C30 and EQ-5D-5L instruments will be used prior to any study treatment and then at protocol-specified time points

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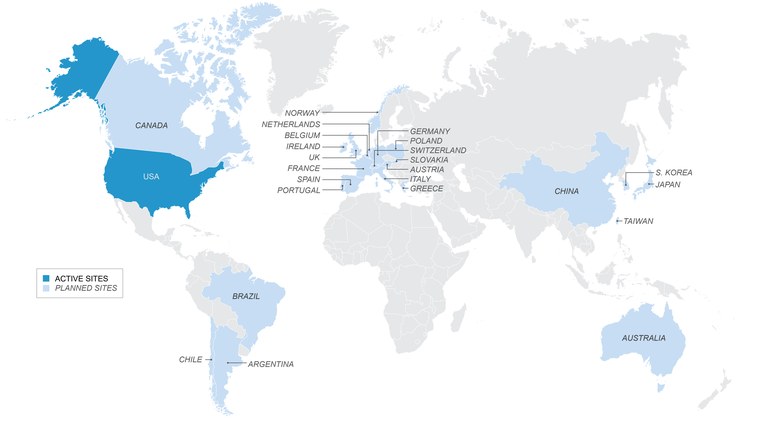
Objectives and Associated Endpoints

Primary Objective	Primary Endpoint
Compare PFS per RECIST v1.1 by BICR assessment between treatment arms	PFS per RECIST v1.1 by BICR assessment
Key Secondary Objectives	**Key Secondary Endpoints**
Evaluate activity in treatment arms	OS, cORR per RECIST v1.1 by BICR and INV assessments, PFS per RECIST v1.1 by INV assessment, DOR per BICR and INV assessments
Evaluate time from randomization to disease progression on next-line treatment or death from any cause (PFS2)	Time from randomization to disease progression on next-line treatment or death from any cause (PFS2)
Assess the overall safety profiles by treatment arm	Safety, measured by adverse events, abnormalities in vital signs and laboratory values, and frequency of dose holds and dose reductions
Evaluate the PK of tucatinib	PK of tucatinib
Assess key PROs	PROs as assessed by EORTC QLQ-C30

Summary

- MOUNTAINEER-03 is investigating the efficacy and safety of tucatinib in combination with trastuzumab and mFOLFOX6 in comparison to mFOLFOX6 given with or without either bevacizumab or cetuximab as first-line treatment in patients with HER2+ mCRC
- Enrollment began in 2022 and is ongoing in the United States with sites planned globally



Abbreviations

BICR, blinded independent central review; BID, twice per day; BRAF, proto-oncogene B-Raf; cORR, confirmed objective response rate; CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire: EQ-5D-5L, EuroQol 5 dimensions 5 levels; HER2, human epidermal growth factor receptor 2; INV, investigator; mFOLFOX 6, 5-fluorouracil, leucovorin, and oxaliplatin; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression free survival; PFS2, time from randomization to disease progression on next-line treatment or death from any cause; PK, pharmacokinetics; PO, orally; PROs, patient-reported outcomes; Q2W, every 2 weeks; Q3W, every 3 weeks; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; WT, wild-type

Disclosures

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Thierry Andre, thierry.andre@aphp.fr