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

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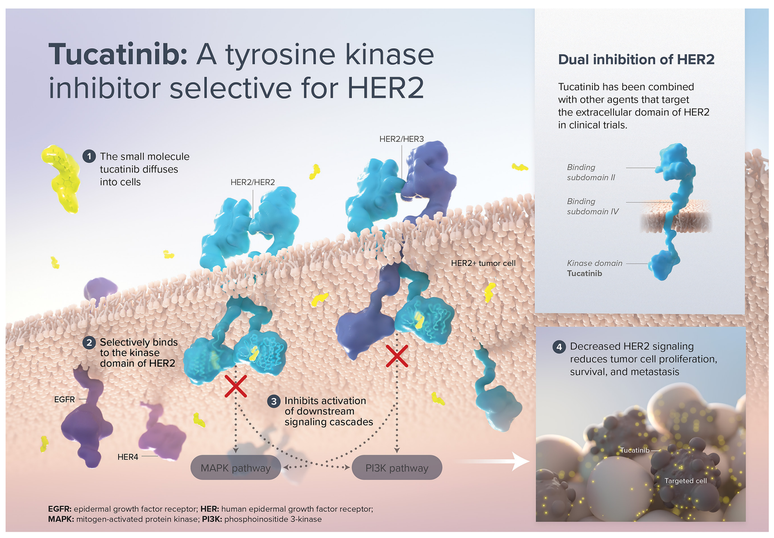
Background and Rationale

- 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 go on to 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, with a higher incidence, of approximately 10%, in those with RAS WT tumors[6–10]
- HER2 alterations have been identified as potential mechanisms of primary resistance and poor response to anti-EGFR therapies[9,11–14]
- 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 and is being investigated in gastrointestinal cancers[16]
  - Results from the primary 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[17]
    - » cORR of 38.1%, median DOR per BICR of 12.4 months
      - ▫ Median duration of follow-up of 16.3 months for all patients and 20.7 months for patients treated with tucatinib and trastuzumab
    - » Tucatinib plus trastuzumab was well tolerated with a low discontinuation rate (5.8%) and no deaths due to AEs
      - ▫ Most common AE was diarrhea, which was predominately low grade (Grade 3 events, 3.5% and no Grade 4 events)
- Based on the results of MOUNTAINEER, tucatinib plus trastuzumab is the first treatment option to be approved by the FDA for patients with chemotherapy-refractory, HER2+, RAS WT mCRC

Tucatinib Proposed Mechanism of Action



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

Key Inclusion Criteria

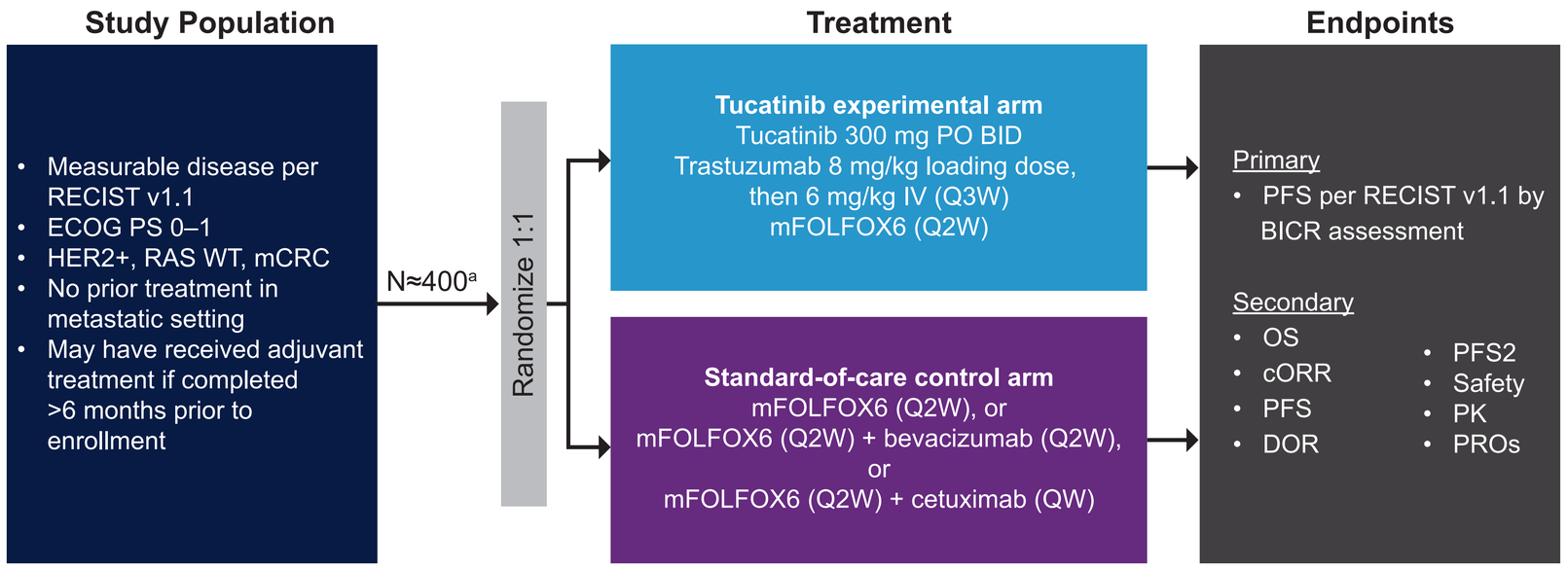
- Histologically and/or cytologically documented adenocarcinoma of the colon or rectum, which is metastatic or unresectable
- HER2+ disease, determined centrally using a tissue-based HER2 assay
- *RAS* wild-type mCRC, determined locally or centrally
- ≥18 years
- Measurable disease per RECIST v1.1
-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

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

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



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

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, and 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 AEs, abnormalities in vital signs and laboratory values, and frequency of dose holds, dose reductions, and treatment discontinuations
Evaluate the PK of tucatinib	Plasma concentrations of tucatinib
Assess key PROs	PROs as assessed by EORTC QLQ-C30

Key Study Assessments

Efficacy

- Radiological disease assessments (CT and/or MRI) will be performed at screening/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

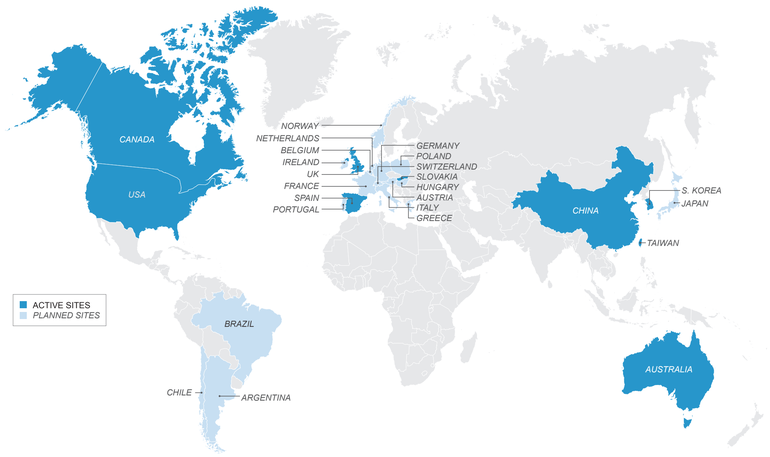
- Laboratory Assessments will be performed locally

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

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, Canada, Spain, Slovakia, United Kingdom, Australia, South Korea, China, and Taiwan



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Abbreviations

AE, adverse event; BICR, blinded independent central review; BID, twice per day; BRAF, proto-oncogene B-Raf; cORR, confirmed objective response rate; CRC, colorectal cancer; CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5 dimensions 5 levels; FDA, United States Food and Drug Administration; HER2, human epidermal growth factor receptor 2; INV, investigator; MAPK, mitogen-activated protein kinase; mCRC, metastatic colorectal cancer; mFOLFOX6, 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; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetics; PO, orally; PROs, patient-reported outcomes; Q2W, every 2 weeks; Q3W, every 3 weeks; QW, once weekly; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; WT, wild-type

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