MOUNTAINEER: Open-Label, Phase 2 Study of Tucatinib Combined with Trastuzumab for HER2-Positive Metastatic Colorectal Cancer

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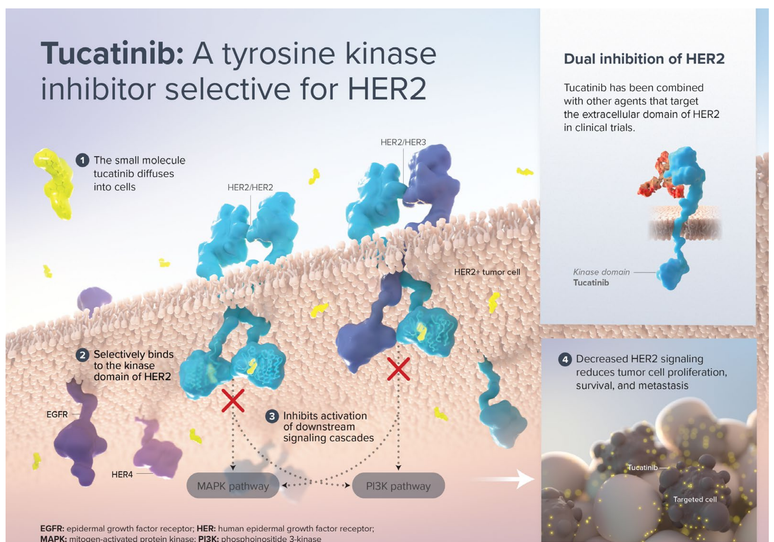
Background and Rationale

- Colorectal cancer (CRC) is one of the most common malignancies worldwide, ranking globally as the third most common cancer with approximately 1.8 million new cases per year. It is the second leading cause of cancer deaths in the US and worldwide, with approximately 50,000 and 900,000 deaths per year, respectively.[1,2]
- Based on current treatment algorithms, survival for patients with metastatic CRC (mCRC) is approximately 2-3 years.[3-6]
- Human epidermal growth factor receptor 2 (HER2) is a validated target in breast and gastric cancers.
  - Monoclonal antibodies (mAb) and small-molecule tyrosine kinase inhibitors (TKI) are approved for breast cancer and mAb for gastric cancer.
- There is growing interest in exploring HER2-targeting strategies for patients with mCRC, where amplification occurs in approximately 3-5% of patients.
  - HER2 amplification is more common in RAS wild-type patients, with up to 5-14% prevalence.[7]
  - RAS mutant patients may be more resistant to anti-HER2-targeting strategies.[8]
- Tucatinib is an oral, small-molecule TKI.
  - Highly selective for HER2 with minimal inhibition of epidermal growth factor receptor (EGFR)[9]
- In patient-derived xenograft models of HER2+ mCRC, the combination of tucatinib + trastuzumab showed significantly greater antitumor activity compared with either agent alone.[10]
- Non-randomized studies conducted in patients with HER2+ metastatic CRC have demonstrated the efficacy and tolerability of dual HER2-blockade.[4,7]
- This trial is designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab in patients with HER2+ mCRC.

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.

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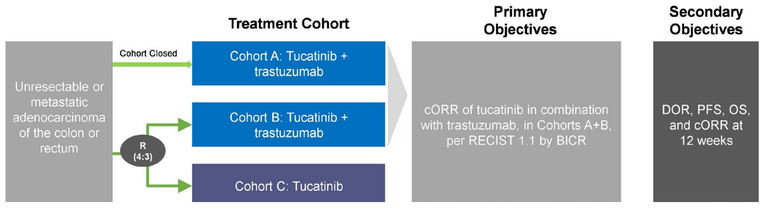
Study Design

- MOUNTAINEER (NCT03043313, EudraCT no. 2020-000540-60) is an open-label, pivotal phase 2 study that initially consisted of a non-randomized cohort of 45 patients (Cohort A; now closed), treated with tucatinib (300 mg BID) and trastuzumab (8 mg/kg IV followed by 6 mg/kg IV every 3 weeks).
- To enable better estimation of objective response rate and safety, the study was expanded to include 70 additional patients randomized 4:3 into 2 cohorts:
  - Cohort B (N=40) will receive tucatinib + trastuzumab.
  - Cohort C (N=30) will receive tucatinib monotherapy.
    - Patients in Cohort C will be initially treated with tucatinib (300 mg orally twice daily [PO BID]).
    - Patients will have the option to crossover to tucatinib + trastuzumab if an objective response is not achieved by 12 weeks, or if progressive disease develops at any time.



Abbreviations: BICR=blinded independent central review, cORR=confirmed objective response rate, DOR=duration of response, OS=overall survival, PFS=progression-free survival, RECIST=Response Evaluation Criteria in Solid Tumors

Key Eligibility Criteria

- Adenocarcinoma of the colon or rectum that is metastatic and/or unresectable
- Prior therapy containing the following agents: fluoropyrimidine, oxaliplatin, irinotecan, an anti-VEGF monoclonal antibody, and an anti-PD-(L)1 therapy if tumor has deficient mismatch repair proteins or is microsatellite instability-High
- Patients that have received prior anti-HER2 targeted therapies are not eligible
- Have RAS wild-type in primary or metastatic tumor tissue, based on expanded RAS testing
- Local laboratory confirmation of HER2+ mCRC as determined by immunohistochemistry (IHC), in situ hybridization (ISH) assay, or tissue-based next-generation sequencing (NGS) assay
- At least one site of disease measurable by RECIST v1.1 criteria
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2

Study Assessments

- Efficacy
  - Radiographic assessment of tumor response per RECIST v1.1
- Pharmacokinetics
  - From baseline through Cycle 6
- Exploratory biomarkers
  - Assessment of HER2 status in tissue by IHC and Fluorescence in situ hybridization (FISH)
  - Assessment of HER2 status in blood and tissue by NGS
- Patient-reported outcome measures using the EORTC QLQ-C30
- Health economic assessments using the EQ-5D-5L instrument and health resource utilization
- Safety and tolerability

Study Endpoints

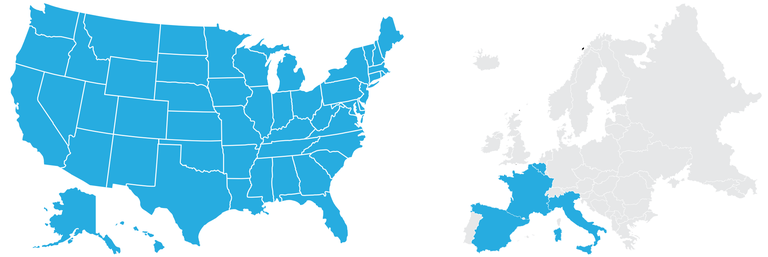
Primary

- cORR per RECIST v1.1 per BICR in pooled Cohorts A+B

Secondary

- Efficacy
  - ORR at 12 weeks of treatment per RECIST v1.1 according to BICR assessment in pooled Cohorts A+B, and Cohort C
  - DOR per RECIST v1.1 according to BICR assessment in pooled Cohorts A+B, and Cohort C
  - PFS per RECIST v1.1 according to BICR assessment for pooled Cohorts A+B
  - OS in pooled Cohorts A+B
- Safety and tolerability
  - Incidence of adverse events (AEs)
  - Incidence of dose modifications
  - Incidence of laboratory abnormalities

Study Sites



- Enrollment is ongoing in the US and planned in the EU.
- Total number of planned global sites: approximately 55

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