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

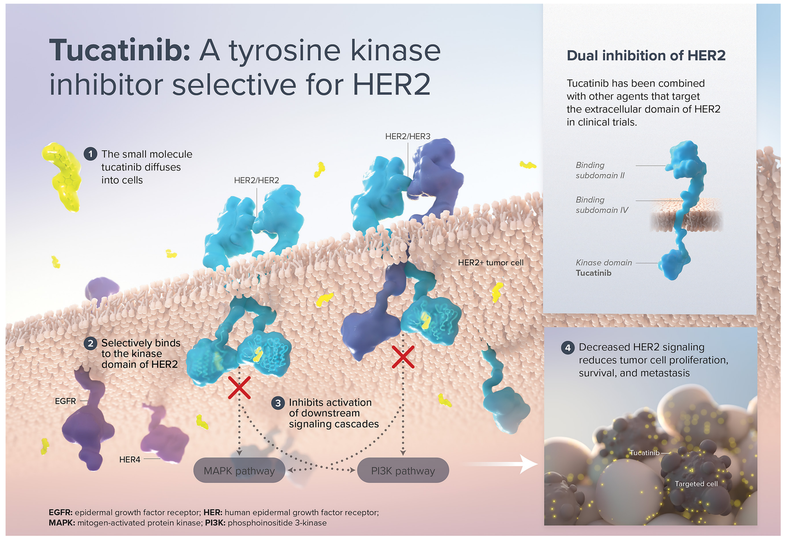
Tanios Bekaii-Saab[1], Erik Van Cutsem[2], Josep Tabernero[3], Salvatore Siena[4], Takayuki Yoshino[5], Yoshiaki Nakamura[5], Kanwal Raghav[6], Andrea Cercek[7], Volker Heinemann[8], David Adelberg[9], James Ward[10], Shan Yang[10], Thierry Andre[11], John Strickler[12]

[1]Mayo Clinic, Scottsdale, AZ, USA; [2]University Hospital Gasthuisberg and University of Leuven, Leuven, Belgium; [3]Vall D'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; [4]Grande Ospedale Metropolitano Niguarda and Università degli Studi di Milano, Milan, Italy; [5]National Cancer Center Hospital Japan East, Kashiwa, Japan; [6]MD Anderson Cancer Center, Houston, TX, USA; [7]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [8]University of Munich, Munich, Germany; [9]Merck & Co., Inc., Rahway, NJ, USA; [10]Seagen Inc., Bothell, WA, USA; [11]Sorbonne Université et INSERM 'Instabilité des Microsatellites et Cancer, Hôpital Saint Antoine, Paris, France; [12]Duke University Medical Center, Durham, NC, USA

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 and approximately 5%–14% of patients with *RAS/BRAF* wild-type mCRC[6–10]
- HER2 alterations have been identified as potential mechanisms of primary resistance and poor response to anti-EGFR therapies[9,11–14]
  - There are currently no FDA- or EMA-approved therapies for HER2+ mCRC
- 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[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)

Tucatinib Proposed Mechanism of Action

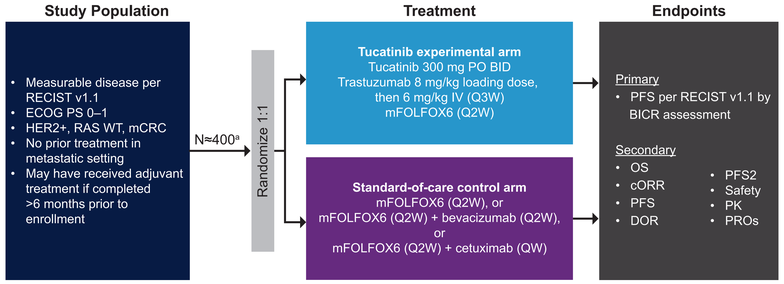


Tucatinib is an investigational agent, and its safety and efficacy have not been established. There is no guarantee that tucatninb will receive regulatory approval and become commercially available for uses being investigated.

© 2023 Seagen Inc. Bothell WA 98021. All rights reserved. USM/TUC/2019/0018

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)

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 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

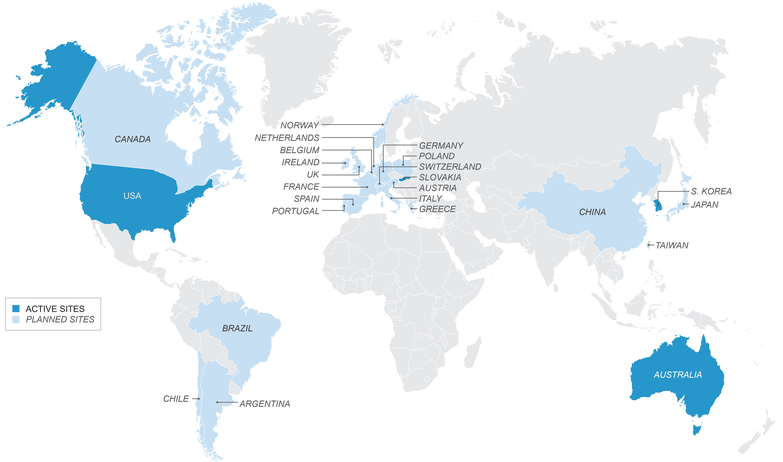
- The EORTC QLQ-C30 and EQ-5D-5L instruments will be used prior to any study treatment and then at protocol-specified time points

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

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, Slovakia, South Korea, and Australia



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

Disclosures

This study is sponsored by Seagen Inc., Bothell, WA, USA, in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. TBS: Research Funding / Grants: Abgenomics, Agios, Arcus, Arys, Atreca, Bayer, BMS, Boston Biomedical, Celgene, Clovis, Eisai, Genentech, Incyte, Ipsen, Lilly, Merus, Mirati, Novartis, Pfizer, Seagen Inc.; Consulting or Advisory Role: AbbVie, Amgen, Aptitude Health, Arcus, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Celularity, Daichii Sankyo, Daichii Sankyo/UCB Japan, Decipherra, Eisai, Exact, Foundation, Genentech, Janssen, Illumina, Immuneering, Incyte, Ipsen, Kanaph, Lilly, Merck, MJH Life Sciences, Natera, Pfizer, Roche/Genentech, Seagen Inc., Sobi, Stemline, Treos; IDMC/DSMB: 1Globe; AstraZeneca, Exelixis, FibroGen, Merck/Eisai, PanCan, Suzhou Kintor; Scientific Advisory Board: Artiva, Immuneering, Imugene, Replimune, Sun Biopharma, Xilis; Royalties: UpToDate; Inventions/Patents: WO/2018/183488, WO/2019/055687; Other Relationship: Lilly, Merck, Pancreatic Cancer Action Network. JW: Employment: AbbVie, Seagen Inc.; Travel Expenses: AbbVie, Seagen Inc.; Equity Ownership: AbbVie, Seagen Inc. SY: Employment: Merck, Seagen Inc.; Equity Ownership: Merck, Seagen Inc.

Acknowledgements

Thank you to our patients and their families for their participation and to all research personnel for their support of this important trial. Under the guidance of the authors, assistance in medical writing was provided by Irina Mordukhovich, PhD, of MMS Holdings (Canton, MI, USA) and was funded by Seagen Inc. in accordance with Good Publication Practice guidelines.

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® or the author of this poster, **Tanios Bekaii-Saab, bekaii-saab.tanios@mayo.edu**

References

1. Baidoun F, Elshiwy K, Elkeraie Y, et al. Curr Drug Targets. 2021;22(9):998-1009.
2. Cancer Stat Facts: Colorectal Cancer. National Cancer Institute. Updated 2019. Accessed January 4, 2023. https://seer.cancer.gov/statfacts/html/colorect.html
3. Kahi CJ, Boland CR, Dominitz JA, et al. Gastroenterology 2016;150:758–768.e11.
4. Heinemann V, Singh M, Hardstock F, et al. Clin Colorectal Cancer. 2022;21(2):122-131.
5. Van Cutsem E, Cervantes A, Adam R, et al. Ann Oncol. 2016;27(8):1386-1422.
6. Benson AB, Venook AP, Al-Hawary MM, et al. J Natl Compr Canc Netw. 2021;19(3):329-359.
7. Kang A, Bloudek L, Mordi U, et al. J Manag Care Spec Pharm. 2021;S20-21.
8. Patel JN, Fong MK, Jagosky M. J Pers Med. 2019;9(1):3.
9. Sartore-Bianchi A, Amatu A, Porcu L, et al. The Oncologist. 2019;24(10):1395-1402.
10. Strickler JH, Ng K, Cercek A, et al. J Clin Oncol. 2021;39(3 Suppl):Abstract TPS153.
11. Bertotti A, Papp E, Jones S, et al. Nature. 2015;526:263-267.
12. Jeong JH, Kim J, Hong YS, et al. Clin Colorectal Cancer. 2017;16(3):e147-152.
13. Raghav K, Loree JM, Morris JS, et al. JCO Precis Oncol. 2019;3:1-13.
14. Sawada K, Nakamura Y, Yamanaka T, et al. Clin Colorectal Cancer. 2018;17(3):198-205.
15. Kulukian A, Lee P, Taylor J, et al. Mol Cancer Ther. 2020;19(4):976-987.
16. TUKYSA [prescribing information]. Bothell, WA: Seagen, Inc.; 2021.
17. Strickler J, Cercek A, Siena S, et al. Ann Oncol. 2022;33(Suppl 4):S375-376.

Abstract No. TPS261
American Society of Clinical Oncology Gastrointestinal Cancers Symposium, January 19–21, 2023