MOUNTAINEER-02: PHASE 2/3 STUDY OF TUCATINIB, TRASTUZUMAB, RAMUCIRUMAB, AND PACLITAXEL IN PREVIOUSLY TREATED HER2+ GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (GEC): (TRIAL IN PROGRESS)

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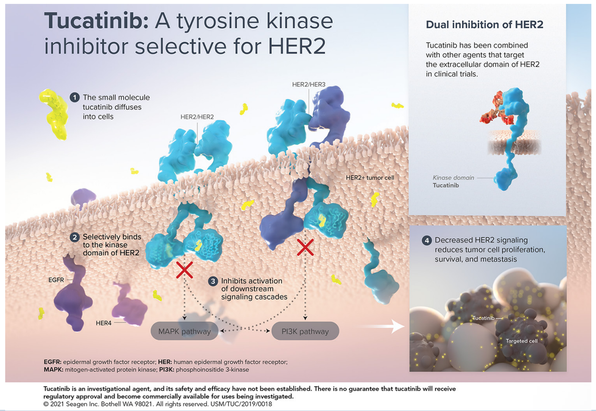
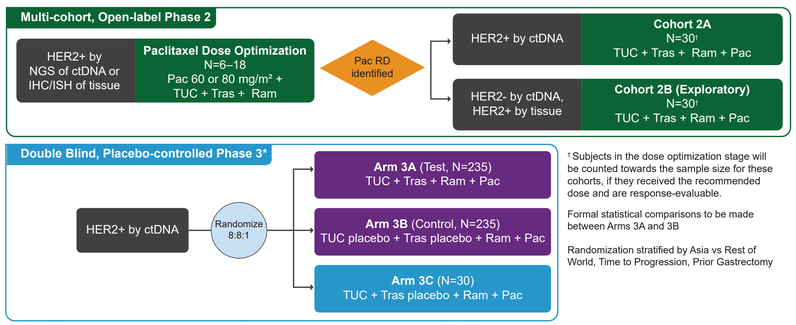
Background and Rationale

- Tucatinib is a highly selective HER2-directed TKI with minimal EGFR inhibition recently approved in the US, Europe, and other countries for HER2+ MBC[1]
- It is being developed as a novel therapy for patients with mCRC and other GI tumors
- Trastuzumab with chemotherapy is standard in the 1st-line setting for metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma (GEC)
- However, no anti-HER2 therapy has demonstrated an OS benefit over chemotherapy in 2nd-line, possibly due to loss of HER2 expression following trastuzumab-based therapy
- In gastric and esophageal patient-derived and cell line-derived xenograft models, dual targeting of HER2 with tucatinib and trastuzumab showed superior activity to either agent alone[2]
- The pivotal HER2CLIMB study clearly demonstrated the benefit of adding tucatinib to trastuzumab and capecitabine in HER2+ MBC[1]
- Interim results from the MOUNTAINEER study have shown promising activity for tucatinib and trastuzumab in HER2+ mCRC[3]
- The MOUNTAINEER-02 study will combine the dual HER2-inhibition of tucatinib and trastuzumab with standard of care therapy in the 2nd-line setting for patients with HER2+ GEC

Tucatinib Proposed Mechanism of Action[2]



Study Design



† Subjects in the dose optimization stage will be counted towards the sample size for these cohorts, if they received the recommended dose and are response-evaluable.

Formal statistical comparisons to be made between Arms 3A and 3B

Randomization stratified by Asia vs Rest of World, Time to Progression, Prior Gastrectomy

* The SMC may recommend proceeding to phase 3 if the regimen is safe and tolerable and an ORR ≥36% is observed in all response-evaluable patients treated at the Pac RD who have HER2+ disease by NGS assay of ctDNA.

Study Objectives and Endpoints – Phase 2

Phase 2 Primary Objectives	Endpoints
Determine the RD of paclitaxel	Frequency of DLT during the first cycle of treatment
Safety and tolerability of Phase 2 regimen	Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities; vital signs and other relevant safety variables; frequency of dose modifications
Secondary Objectives	**Endpoints**
Evaluate preliminary activity in Cohort 2A	ORR, confirmed ORR, PFS, DOR, and DCR per investigator
Evaluate PK of tucatinib, paclitaxel, and their metabolites	The PK parameters to be calculated may include but are not limited to: AUC, AUC_{last}, C_{max}, T_{max}, C_{trough}, MR_{AUC}

Exploratory objectives are preliminary activity in Cohort 2B, correlations between HER2 alterations detected by different assays, correlation between blood-based biomarkers and clinical outcomes, PK in patients with gastrectomies

Study Objectives and Endpoints – Phase 3

Phase 2 Primary Objectives	Endpoints
Compare efficacy of TUC and trastuzumab (Arm 3A) vs placebo (Arm 3B), both with ramucirumab + paclitaxel	• **Dual primary endpoints:** OS and PFS per investigator • **Key secondary endpoint:** Confirmed ORR per investigator • **Other secondary endpoints:** PFS, confirmed ORR, ORR, DOR, DCR per BICR; ORR, DOR, DCR per investigator
Secondary Objectives	**Endpoints**
Evaluate safety and tolerability of tucatinib + trastuzumab + ramucirumab + paclitaxel	Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities; vital signs and other relevant safety variables; frequency of dose modifications

Other secondary and exploratory objectives are to evaluate PROs by arm, evaluate the activity, safety and tolerability of tucatinib + ramucirumab + paclitaxel, evaluate the PK of tucatinib, evaluate correlations between biomarkers and outcomes, and assess HCRU by arm

Study Treatment

	Dose	Route	28-day cycle		
			Day 1	Day 8	Day 15
Tucatinib	300 mg	PO	BID every day		
Tucatinib placebo		PO	BID every day		
Trastuzumab	6 mg/kg loading dose 4 mg/kg other infusions	IV	x		
Trastuzumab placebo		IV	x		x
Ramucirumab	8 mg/kg	IV	x		x
Paclitaxel	60 or 80 mg/m²	IV	x	x	x

Abbreviations: antibody-drug conjugate; AE: adverse event; AUC: area under the plasma concentration-time curve; AUC_{last}: AUC to the time of the last quantifiable concentration; BICR: blinded independent central review; BID: twice daily; C: cycle; CBC: complete blood count; C_{max}: maximum observed concentration; CNS: central nervous system; CR: complete response; ctDNA: circulating tumor DNA; C_{trough}: trough concentration; D: day; DCR: disease control rate (CR or PR or stable disease/non-CR, non-progressive disease as best objective response); DDI: drug-drug interaction; DLT: dose limiting toxicity; DOR: duration of response; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; EGFR: endothelial growth factor receptor; EOT: end of treatment; GEC: gastric or gastroesophageal junction adenocarcinoma; GI: gastrointestinal; HCRU: healthcare resource utilization; HER2: human epidermal growth factor receptor 2; HER2+: HER2 overexpression or amplification; IHC: immunohistochemistry; ISH: in situ hybridization; IV: intravenous; LVEF: left ventricular ejection fraction; MBC: metastatic breast cancer; mCRC: metastatic colorectal cancer; MR_{AUC}: metabolic ratio based on AUC; NGS: next generation sequencing; ORR: objective response rate (CR or PR); OS: overall survival; Pac: paclitaxel; PK: pharmacokinetics; PFS: progression-free survival; PO: orally; PR: partial response; PRO: patient-reported outcomes; Ram: ramucirumab; RD: recommended dose; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SMC: Safety Monitoring Committee; TKI: tyrosine kinase inhibitor; T_{max}: time of C_{max}; Tras: trastuzumab; TUC: tucatinib.

Disclosures: This study is sponsored by Seagen Inc., Bothell, WA, USA in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. DC, JT, YYJ, TSB-S, SS have consulting or advisory roles with Seagen Inc. DC received honoraria from Seagen Inc. JHS is on an advisory board and is a principal investigator for Seagen Inc. JGM, MCP-W, DX are employees of and own stock in Seagen Inc.

Eligibility: Key Inclusion Criteria

Key Inclusion Criteria

- Histologically or cytologically confirmed locally-advanced unresectable or metastatic GEC, excluding squamous cell or undifferentiated GEC
- HER2+ disease, documented since progression of most recent systemic therapy:

Phase 2 Dose Optimization	HER2+ in NGS assay of ctDNA or IHC/ISH assay of tissue
Phase 2 Cohort 2A	HER2+ in NGS assay of ctDNA
Phase 2 Cohort 2B	HER2- in NGS assay of ctDNA, HER2+ in IHC/ISH assay of tissue
Phase 3	HER2+ in NGS assay of ctDNA

- Progression during or after 1st-line therapy, and have received a HER2-directed antibody
- ≥18 years of age
- Measurable disease per RECIST v1.1 (phase 2 only)
- ECOG performance status ≤1
- Adequate hepatic, hematological, renal, and cardiac function

Key Exclusion Criteria

- >1 line of prior therapy for advanced disease
- Prior ramucirumab, anti-HER2 or anti-EGFR TKIs, HER2-directed ADCs; taxanes ≤12 months before enrollment
- Positive for hepatitis B or C
- Active CNS metastases

Phase 3 Analysis

- The dual primary endpoints will be evaluated using parallel testing, with α recycling if only one meets statistical significance. An interim OS analysis is planned at the time of the final PFS analysis. Arm 3A and Arm 3B sample size of 470 subjects maintains 90% power for PFS with an α of 0.02, and 88% power for OS with an α of 0.03

Study Assessments

- Disease assessments per RECIST v1.1: q6 weeks for 36 weeks, then q9 weeks. After discontinuation, assessments are q9 weeks until disease progression, withdrawal of consent, death, or study closure
- Safety assessments: AEs, SAEs, events of interest, treatment modifications, laboratory assessments (metabolic panel, CBC with differential, eGFR, and coagulation panel), vital signs, LVEF every 12 weeks, and ECG at baseline and EOT
- Phase 2 PK assessments (blood draws on C1D1, D8, and C2D1):
  - Dose optimization stage: serial PK to assess tucatinib-paclitaxel DDI
  - Dose expansion stage: serial PK in first 6 subjects with gastrectomy to assess impact on tucatinib PK
- Biomarker assessments: screening HER2 status by NGS of ctDNA and tissue and IHC/ISH of tissue; blood sample for other biomarkers at screening and EOT

Summary

- MOUNTAINEER-02 is a phase 2/3 study evaluating tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in previously-treated patients with advanced HER2+ GEC
- Approximately 180 sites are planned in North America, Asia-Pacific, and Europe. The study is open and enrolling.

References

1. Murthy et al NEJM 2020
2. Kulukian et al, Mol Cancer Ther. 2020
3. Strickler et al, Ann Oncol. 2019

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