

# MOUNTAINEER-02: Phase 2/3 Study of Tucatinib, Trastuzumab, Ramucirumab, and Paclitaxel in Previously Treated HER2+ Gastric or Gastroesophageal Junction Adenocarcinoma (Trial in Progress)

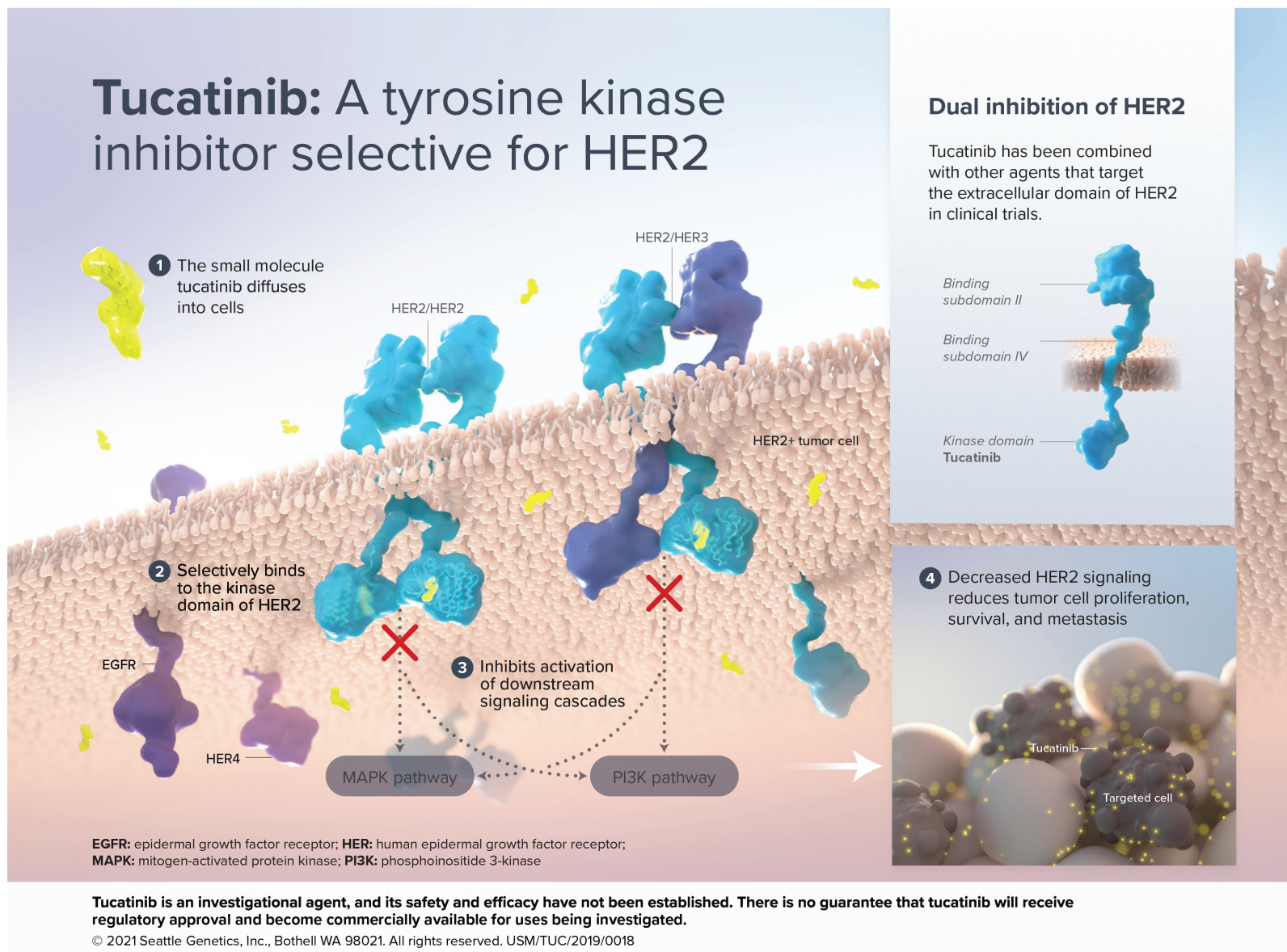
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## Background and Rationale

- Tucatinib (TUC) is a highly selective HER2-directed TKI recently approved for HER2+ MBC
- It is being developed as a novel therapy for patients with mCRC and other GI tumors
- Trastuzumab (Tras) 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 Tras-based therapy
- In gastric and esophageal patient-derived and cell line-derived xenograft models, dual targeting of HER2 with TUC and Tras showed superior activity to either agent alone<sup>1</sup>
- The pivotal HER2CLIMB study clearly demonstrated the benefit of adding TUC to Tras and capecitabine in HER2+ MBC<sup>2</sup>
- Interim results from the MOUNTAINEER study have shown promising activity for TUC and Tras in HER2+ mCRC<sup>3</sup>
- The MOUNTAINEER-02 study will combine the dual HER2-inhibition of TUC and Tras with standard of care therapy in the 2nd-line setting for patients with HER2+ GEC

## Tucatinib Proposed Mechanism of Action



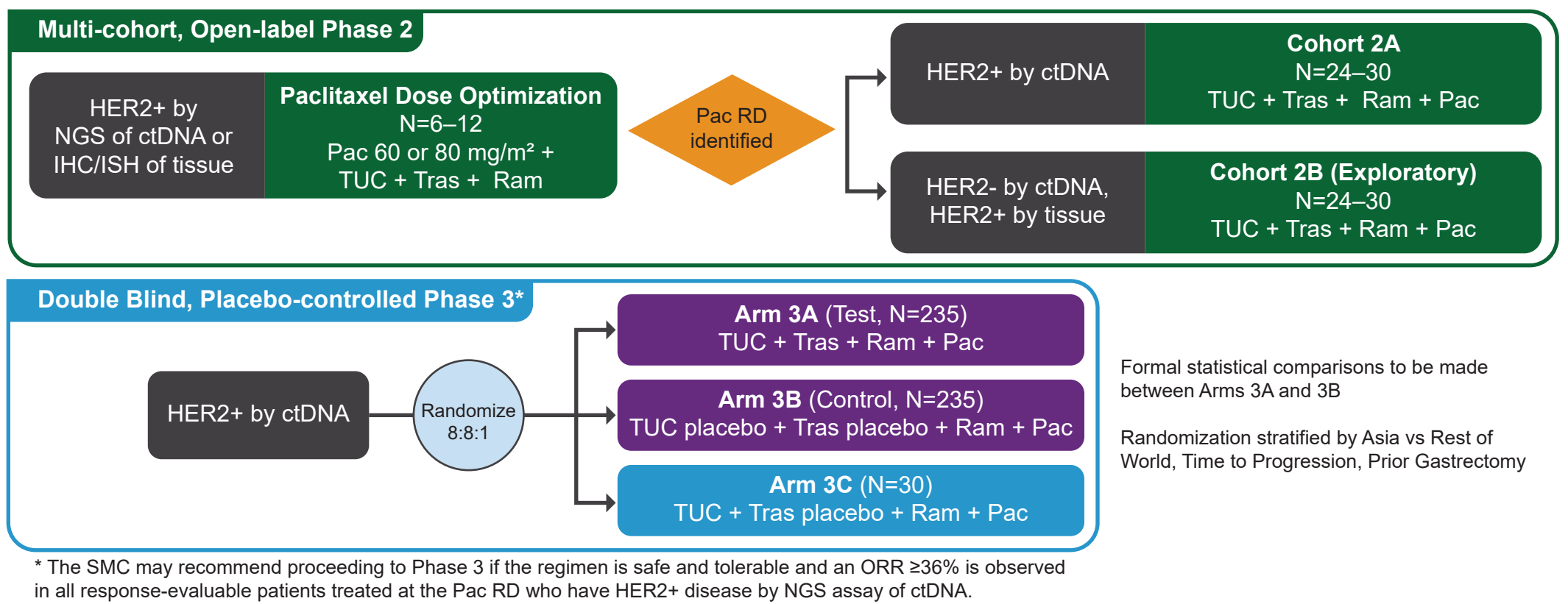
## Study Treatment

	Dose	Route	28-day cycle		
			Day 1	Day 8	Day 15
TUC	300 mg	PO		BID every day	
TUC placebo		PO		BID every day	
Tras	6 mg/kg loading dose 4 mg/kg other infusions	IV	X		X
Tras placebo		IV	X		X
Ram	8 mg/kg	IV	X		X
Pac	60 or 80 mg/m <sup>2</sup>	IV	X	X	X

ADC: antibody-drug conjugate; AE: adverse event; AUC: area under the plasma concentration-time curve; AUC<sub>0-∞</sub>: AUC to the time of the last quantifiable concentration; BICR: blinded independent central review; BID: twice daily; C: cycle; CBC: complete blood count; C<sub>max</sub>: maximum observed concentration; CNS: central nervous system; CR: complete response; ctDNA: circulating tumor DNA; C<sub>trough</sub>: 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; ECOG: 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<sub>0-∞</sub>: 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<sub>max</sub>: time of C<sub>max</sub>; Tras: trastuzumab; TUC: tucatinib.

## 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

## Study Design



## Eligibility

### Key Inclusion Criteria

- Histologically or cytologically confirmed locally-advanced unresectable or metastatic GEC, excluding squamous cell or undifferentiated GEC
- HER2+ disease, (performed or confirmed by central assessment):

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 Ram, 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 Comparison

- 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

## Objectives and Endpoints – Phase 2

Phase 2 Primary Objectives	Endpoints
Determine the RD of Pac	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 TUC, Pac, and their metabolites	The PK parameters to be calculated may include but are not limited to: AUC, AUC <sub>last</sub> , C <sub>max</sub> , T <sub>max</sub> , C <sub>trough</sub> , MR <sub>AUC</sub>

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

## Objectives and Endpoints – Phase 3

Phase 3 Primary Objectives	Endpoints
Compare efficacy of TUC and Tras (Arm 3A) vs placebo (Arm 3B), both with ramucirumab (Ram) + paclitaxel (Pac)	<ul style="list-style-type: none"><li>Dual primary endpoints: OS and PFS per investigator</li><li>Key secondary endpoint: Confirmed ORR per investigator</li><li>Other secondary endpoints: PFS, confirmed ORR, ORR, DOR, DCR per BICR; ORR, DOR, DCR per investigator</li></ul>
Secondary Objectives	Endpoints
Evaluate safety and tolerability of TUC + Tras + Ram + Pac	Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities; vital signs and other relevant safety variables; frequency of dose modifications
Evaluate anti-tumor activity of TUC + Ram + Pac (Arm 3C)	Confirmed ORR, DOR per investigator

Other secondary and exploratory objectives are to evaluate PROs by arm, evaluate safety and tolerability of TUC + Ram + Pac, evaluate the PK of TUC, evaluate correlations between biomarkers and outcomes, and assess HCRU by arm

## 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 TUC-Pac DDI
  - Dose expansion stage: serial PK in first 6 subjects with gastrectomy to assess impact on TUC 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

## Study Status

- The study is open and enrolling, with an estimated study end date of June 2025. Approximately 180 sites are planned in North America, Asia-Pacific, and Europe. The evaluation of the Pac 60 mg/m<sup>2</sup> dose level is ongoing

### References

- Kulukian et al, Mol Cancer Ther. 2020;19(4):976-987
- Murthy et al, N Engl J Med. 2020;382(7):597-609
- Strickler et al, Ann Oncol. 2019;30(Suppl 5):v200

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