SGNTUC-019: Phase 2 Basket Study of Tucatinib and Trastuzumab in Previously Treated Solid Tumors With HER2 Alterations: Urothelial Cancer Cohort (Trial in Progress)

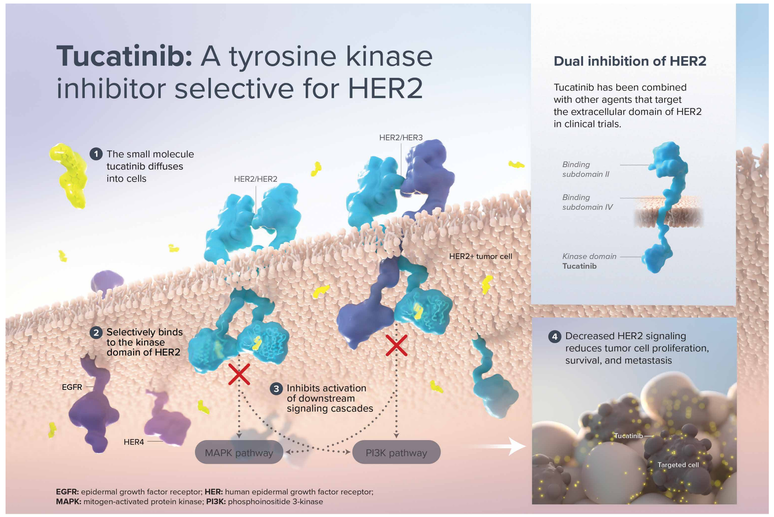
Matt D. Galsky[1], Jorge Ramos[2], Sherry Tan[2], Evan Y. Yu[3]

[1]Icahn School of Medicine at Mount Sinai Hospital, New York, NY; [2]Seagen Inc., Bothell, WA; [3]Division of Oncology, Department of Medicine, University of Washington, Seattle, WA

Background

- Tucatinib (TUC), approved in multiple regions for HER2+ metastatic breast cancer, is a highly selective HER2-directed TKI with minimal EGFR inhibition
- TUC is being investigated as a novel therapy for patients with metastatic colorectal cancer and other GI tumors
- In metastatic urothelial cancer (UC), responses to subsequent therapies are generally low, highlighting the need for additional therapeutic approaches
- Given that 20%–30% of metastatic urothelial cancers have molecular alterations of the ErbB family,[1] further evaluation of HER2-directed therapy is warranted
- The SGNTUC-019 basket study (NCT04579380) is evaluating TUC in combination with trastuzumab in patients with HER2+ or *HER2*-mutated solid tumors, including a cohort of patients with locally advanced unresectable or metastatic UC

Tucatinib Proposed Mechanism of Action



Tucatinib is an investigation 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.

© 2022 Seagen Inc., Bothell WA 98021. All rights reserved. USM/TUC/2019/0018

Study Design

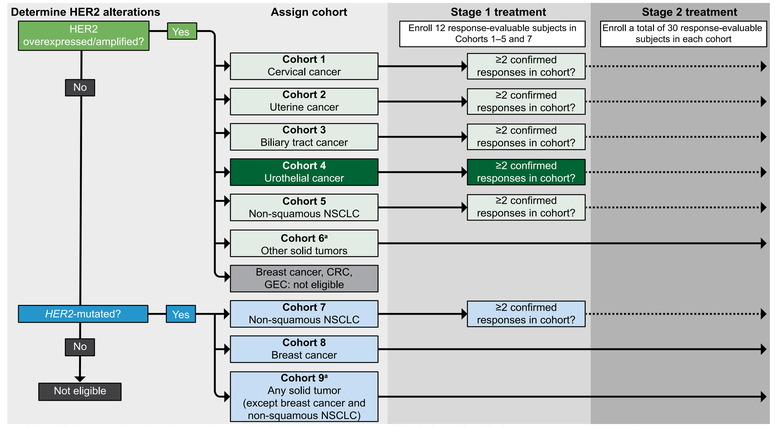
UC Cohorts

- The HER2+ UC cohort (Cohort 4) plans to enroll 12 response-evaluable patients
  - If ≥2 responses are observed, the cohort will be expanded to a total of 30 patients
- Patients with *HER2*-mutated UC will be enrolled into a cohort of 30 patients with other *HER2*-mutated solid tumors (Cohort 9)

Abbreviations

AE: adverse event; AESI: AE of special interest; BC: breast cancer; BID: twice daily; CBC: complete blood count; CNS: central nervous system; CR: complete response; CRC: colorectal cancer; ctDNA: circulating DNA; D: day; DCR: disease control rate (CR or PR or stable disease as best objective response); DOR: duration of response; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; eGFR: estimated glomerular filtration rate; EOT: end of treatment; EQ-5D-5L: European Quality of Life 5-Dimension 5-Level; ErbB: erythroblastic leukemia viral oncogene homolog; GEC: gastric or gastroesophageal junction adenocarcinoma; GI: gastrointestinal; HBV: hepatitis B virus; HCV: hepatitis C virus; HER2: human epidermal growth factor receptor 2; HIV: human immunodeficiency virus; HR+: hormone receptor positive; HRQoL: health-related quality of life; IHC: immunohistochemistry; ISH: in situ hybridization; IV: intravenous; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; NGS: next generation sequencing; NSCLC: non-small cell lung cancer; ORR: objective response rate (CR or PR); OS: overall survival; PFS: progression-free survival; PK: pharmacokinetics; PO: orally; PR: partial response; PRO: patient-reported outcome; q: every; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SMC: safety monitoring committee; TKI: tyrosine kinase inhibitor; TUC: tucatinib; UC: urothelial cancer

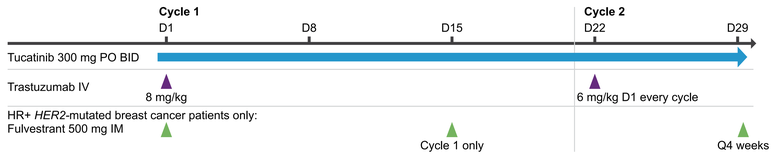
Study Schema



a If a sufficient number of patients with a particular tumor type is enrolled in Cohorts 6 or 9, the sponsor may evaluate that tumor type in a separate, optional cohort.

Study Treatment

- Patients will receive TUC 300 mg PO BID and trastuzumab 8 mg/kg IV on Cycle 1 Day 1 then 6 mg/kg every 21-day cycle



Objectives

Primary Objective	Endpoints
To evaluate the antitumor activity of TUC in combination with trastuzumab	**Primary endpoint:** Confirmed ORR according to RECIST v1.1 per investigator assessment **Secondary endpoints:** DCR, DOR, and PFS per investigator assessment and OS
Secondary Objectives	**Endpoints**
To evaluate the safety and tolerability of TUC in combination with trastuzumab (and with fulvestrant for HR+ *HER2*-mutated BC)	• Incidence, severity, and relatedness of AEs and SAEs • Incidence and severity of laboratory abnormalities • Frequency of dose modifications due to AEs • Other relevant safety variables including AESIs
To evaluate the PK of TUC	Plasma concentrations of TUC
Exploratory Objectives	**Endpoints**
To determine concordance of HER2 alterations by tissue and blood assays	Concordance of HER2 alterations as detected by different testing methodologies
To identify somatic alterations that are associated with resistance to TUC	Identify tumor-specific alterations that are associated with resistance to TUC
To evaluate PROs	Change from baseline in HRQoL based on the EQ-5D-5L

Eligibility

Key Inclusion Criteria

- Histologically or cytologically confirmed, locally-advanced, unresectable or metastatic, HER2+ or *HER2*-mutated solid tumors, including primary brain tumors
- HER2 alterations demonstrated by
  - HER2 overexpression (3+ IHC)
  - *HER2* amplification in tumor tissue by pre-study ISH (signal ratio ≥2.0 or gene copy number >6) or
  - *HER2* amplification or activating mutations in a pre-study or on-study NGS assay of ctDNA or pre-study tissue NGS assay
- Patients with brain metastases may be eligible. Patients in the breast and lung cancer cohorts will undergo baseline brain MRIs
- Measurable disease per RECIST v1.1 according to investigator assessment
- ≥18 years of age
- ECOG performance status 0 or 1
- Adequate hepatic, renal, and hematological functions and LVEF ≥50%
- Patients in the urothelial cohort must have progressed during or after ≥1 prior line of systemic therapy for locally-advanced unresectable or metastatic disease

Key Exclusion Criteria

- HER2+ breast cancer, colorectal cancer, or gastric or gastroesophageal junction adenocarcinoma (GEC)
- Previous HER2-directed therapy
  - Patients with uterine serous carcinoma or *HER2*-mutated GEC without HER2 overexpression/amplification may have previously received trastuzumab
- Myocardial infarction or unstable angina within 6 months or clinically significant cardiopulmonary disease
- Known active HBV, HCV, or HIV infection or chronic liver disease
- CNS lesions characterized by
  - Untreated brain lesions >2.0 cm unless approved by medical monitor
  - Ongoing use of systemic corticosteroids (total daily dose of >2 mg dexamethasone or equivalent) for symptoms of brain lesions
  - Brain lesion thought to require immediate local therapy
  - Known or suspected leptomeningeal disease
  - Generalized/complex partial seizures (>1/week) or neurological progression despite CNS-directed therapy

Assessments

- Disease assessments per RECIST v1.1: q6 weeks for 24 weeks, then q12 weeks. For patients without disease progression at treatment discontinuation, assessments continue until disease progression, withdrawal of consent, death, loss to follow-up, or study closure
- Safety assessments: AEs, SAEs, AESIs, treatment modifications, laboratory assessments (metabolic panel, CBC with differential, and eGFR), vital signs, LVEF every 12 weeks, and ECG at baseline and EOT
  - An SMC will monitor safety at regular intervals
- PK assessments in all patients: Trough TUC concentrations on Cycles 2–6 Day 1 and peak concentrations on Cycle 3 Day 1
- Exploratory biomarker assessments: HER2 status by NGS of ctDNA and tissue IHC/ISH and NGS assays
- EQ-5D-5L questionnaires are administered every 2 cycles during study treatment

Summary

- SGNTUC-019 is a basket study investigating TUC in combination with trastuzumab in previously treated patients with HER2+ or *HER2*-mutated solid tumors, including patients with locally-advanced, unresectable or metastatic UC
- Approximately 75 sites are planned for the US, Asia Pacific, and Europe. The study is open and enrolling in all regions

Reference

1. Koshkin VS et al. Bladder Cancer. 2019;5(1):1-12.

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. **MG:** Consultancy – Aileron Therapeutics, Astellas Pharma, AstraZeneca, BioMotiv, Bristol Myers Squibb, Dendreon, Dracen, Dragonfly Therapeutics, EMD Serono, Genentech, GlaxoSmithKline, Incyte, Inovio Pharma, Janssen, Lilly, Merck, Novartis, NuMab, Pfizer, and Seagen Inc.; Equity Ownership – Rappta Therapeutics; Patents and Royalties – Methods and compositions for treating cancer and related methods. Mount Sinai School of Medicine July 2012 Application number 20120322792; Research Funding/Grants – AstraZeneca, Bristol Myers Squibb, Dendreon, Genentech/Roche, Janssen, Merck, and Novartis. **JR, ST:** Employment and Equity Ownership – Seagen Inc. **EY:** Consultancy – Abbvie, Advanced Accelerator Applications, Bayer, Clovis, Exelixis, Janssen, Merck, and Myovant Sciences; Research Funding/Grants – Bayer, Blue Earth Diagnostics, Daiichi Sankyo, Dendreon, Merck, Seagen, and Taiho.

Abstract No. TPS586
American Society of Clinical Oncology Genitourinary Cancers Symposium 2022; February 17-19, 2022

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, Matt D. Galsky, matthew.galsky@mssm.edu