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

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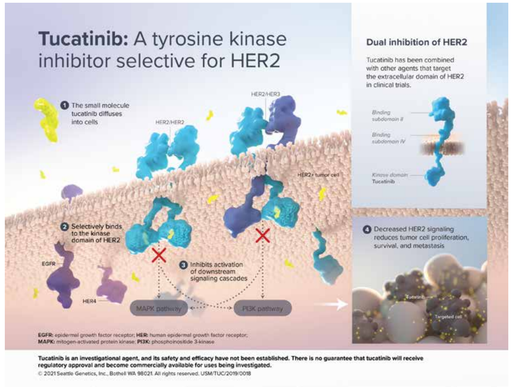
Background and Rationale

- Tucatinib (TUC) is a highly selective HER2-directed TKI recently approved for HER2 overexpressed/amplified (HER2+) metastatic breast cancer
- Tucatinib is in development as a novel therapy for patients with metastatic CRC and other GI tumors
- In HER2+ and HER2-mutated xenograft models, dual targeting of HER2 with the combination of TUC and trastuzumab (Tras) showed superior activity compared to either agent alone[1,2]
- Despite the development of several new therapies for metastatic urothelial cancer, response durations generally remain short and the great majority of patients succumb to the disease, highlighting the need for new therapeutic approaches
- Given that 20-30% of urothelial cancers have molecular alterations of the ErbB family[3], TUC in combination with Tras warrants further evaluation in this population

Tucatinib Proposed Mechanism of Action



Study Design

Urothelial Cancer (UC) Cohort

- In Stage 1, 12 response-evaluable patients with HER2+ UC will be enrolled in Cohort 4
- If ≥2 responses are observed, the posterior probability, according to the PPoS method[4], is >80% that the ORR exceeds 10%. Stage 2 will be opened and a total of 30 response-evaluable patients with HER2+ UC enrolled
- Patients with HER2-mutated UC will be enrolled in Cohort 9; a UC-specific cohort may be opened if enrollment is sufficient

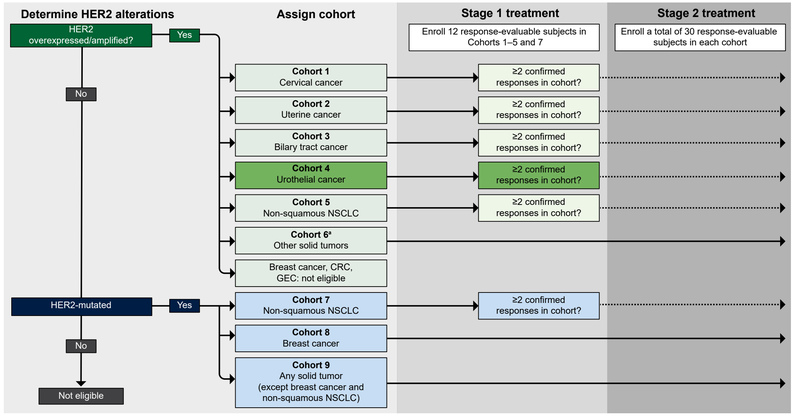
Other Solid Tumors

- Similarly, cohorts for HER2+ cervical, uterine, and biliary tract cancers, and HER2+ and HER2-mutated non-squamous NSCLC will initially enroll 12 patients and be expanded to 30 patients if ≥2 responses are observed
- 30-patient cohorts will enroll other HER2+ solid tumors, HER2-mutated breast cancer, and other HER2-mutated solid tumors
- Patients with HER2+ breast cancer, CRC, or gastric or gastroesophageal junction adenocarcinoma will not be enrolled

AE: adverse event; AESI: AE of special interest; BID: twice daily; CBC: complete blood count; CNS: central nervous system; CR: complete response; CRC: colorectal cancer; ctDNA: circulating DNA; 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: estimated glomerular filtration rate; EOT: end of treatment; EQ-5D-5L: European Quality of Life 5-Dimension 5-Level; GI: gastrointestinal; HBV: hepatitis B virus; HCV: hepatitis C virus; HER2: human epidermal growth factor receptor 2; HER2+: HER2 overexpression or amplification; HIV: human immunodeficiency virus; HRQoL: health-related quality of life; IHC: immunohistochemistry; IM: intramuscular; ISH: in situ hybridization; IV: intravenous; LVEF: left ventricular ejection fraction; NGS: next generation sequencing; NSCLC: non-small cell lung cancer; ORR: objective response rate (CR or PR); OS: overall survival; PK: pharmacokinetics; PFS: progression-free survival; PO: orally; PPoS: predicted probability of success; PR: partial response; PRO: patient-reported outcomes; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SMC: safety monitoring committee; TKI: tyrosine kinase inhibitor; Tras: trastuzumab; TUC: tucatinib; UC: urothelial cancer

SGNTUC-019 is a basket study evaluating tucatinib in combination with trastuzumab in previously treated patients with HER2 overexpressed/amplified or HER2-mutated solid tumors, including a cohort of patients with locally advanced unresectable or metastatic urothelial cancer

Study Schema



Objectives and Endpoints

Primary Objective	Endpoints
To evaluate the antitumor activity of TUC combined with Tras	**Primary endpoint:** Confirmed ORR according to RECIST v1.1 per investigator assessment **Secondary endpoints:** DCR, DOR, and PFS per investigator assessment, and OS
Secondary Objective	**Endpoints**
To evaluate the safety and tolerability of TUC combined with Tras	• 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
Exploratory Objectives	**Endpoints**
To evaluate the PK of TUC	Plasma concentrations of TUC
To explore correlations between tissue and blood-based biomarkers and clinical outcomes	Potential biomarkers of response, resistance, or toxicity may be evaluated in blood and/or tumor tissue
To evaluate PROs	Change from baseline in HRQoL, as assessed by the EQ-5D-5L

Disclosures: Disclosures: EYY has received research funding from Seagen Inc.; EYY, MDG have consulting or advisory roles with Seagen Inc.; VK, LW are employees of Seagen Inc.; LW owns stock in Seagen Inc.; LW is an inventor on a patent held by Seagen Inc.

Eligibility

Key Inclusion Criteria

- Histologically or cytologically confirmed, locally-advanced unresectable or metastatic, HER2+ or HER-mutated solid tumors, including primary brain tumors
- Disease progression on or after the most recent systemic therapy for advanced disease (specific eligibility criteria apply for breast, biliary tract, and cervical cancer, and NSCLC)
- HER2 alterations demonstrated by:
  - HER2+ in tumor tissue by pre-study IHC/ISH (IHC 3+/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
- Measurable disease per RECIST v1.1 according to investigator assessment
- ≥18 years of age
- ECOG performance status 0 or 1
- Adequate hepatic, renal, hematologic, and coagulatory function, and LVEF ≥50%

Key Exclusion Criteria

- HER2+ breast cancer, gastric or gastroesophageal junction adenocarcinoma, or CRC
- Prior HER2-directed therapy; patients with uterine serous carcinoma may have received prior trastuzumab
- Myocardial infarction or unstable angina within 6 months, or clinically significant cardiopulmonary disease
- Known active HBV, HCV, or HIV infection
- Active CNS lesions or chronic liver disease

Study Treatment

- Patients will receive TUC 300 mg PO BID and Tras 8 mg/kg IV on Cycle 1 Day 1 and 6 mg/kg every 21 days thereafter
- Patients with hormone receptor-positive HER2-mutated breast cancer will also receive fulvestrant 500 mg IM once every 4 weeks and on Cycle 1 Day 15

Study Assessments

- Disease assessments per RECIST v1.1: q6 weeks for 24 weeks, then q12 weeks. After 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 tucatinib 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

Study Sites and Completion Dates

- The study is open and enrolling, with an estimated study end date of Q1 2023. Approximately 75 sites are planned in North America, Asia-Pacific, and Europe. US is enrolling all cohorts and Asia-Pacific and Europe are planned.

References

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2. Peterson S et al, AACR. 2020; Abstract 4222
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4. Lee JJ, Liu DD, Clin Trials. 2008; 5(2):93-106

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