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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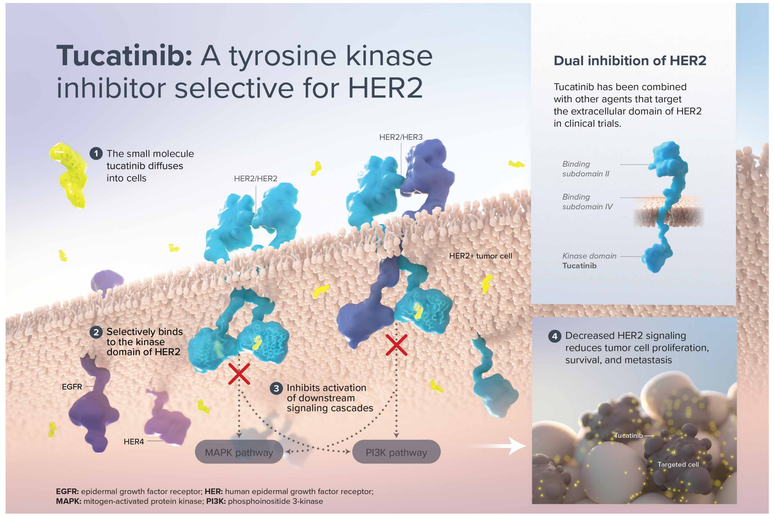
Background

- Tucatinib (TUC), approved in multiple regions for HER2+ metastatic breast cancer, is a highly selective HER2-directed tyrosine kinase inhibitor with minimal EGFR inhibition
- TUC is being investigated as a novel therapy for patients with metastatic colorectal cancer, gastric cancer, and other solid tumors
- Despite development of several new therapies for metastatic urothelial cancer (UC), most patients are refractory to subsequent therapies and die from the disease, 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.

Study Design

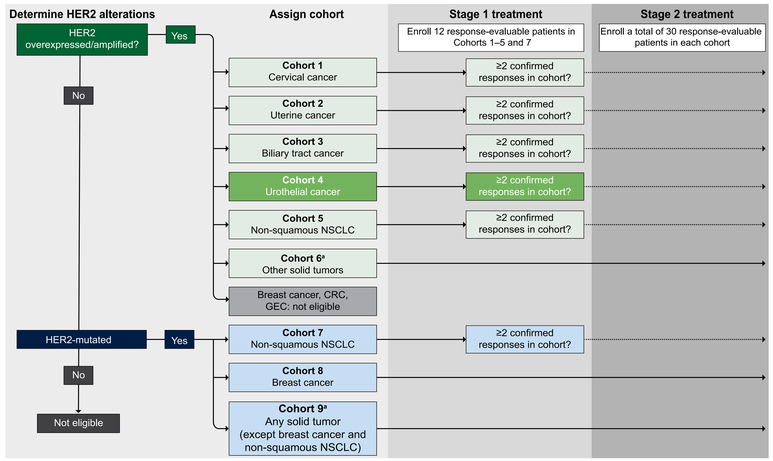
UC Cohort

- 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

Reference

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

Study Schema and Treatment



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 twice a day orally and trastuzumab 8 mg/kg intravenously 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	• 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, HER2+, locally-advanced unresectable or metastatic disease, including primary brain tumors
- HER2 overexpression/amplification demonstrated by
  - *HER2* overexpression (immunohistochemistry 3+)
  - *HER2* amplification in tumor tissue by pre-study in-situ hybridization (signal ratio ≥2.0 or gene copy number >6) or
  - *HER2* amplification in a pre-study or on-study next generation sequencing (NGS) assay of circulating tumor DNA or pre-study tissue NGS assay
- Patients with brain metastases may be eligible
- Measurable disease per RECIST v1.1 according to investigator assessment
- ECOG performance status 0 or 1
- ≥18 years of age
- 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
- Previous HER2-directed therapy
  - Patients with uterine serous carcinoma or HER2-mutated gastric or gastroesophageal junction adenocarcinoma without HER2-overexpression/amplification may have received prior trastuzumab
- Active central nervous system lesions >2 cm, unless approved by the medical monitor
- Myocardial infarction or unstable angina within 6 months or clinically significant cardiopulmonary disease
- Known active HBV, HCV, HIV infection or chronic liver disease

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

Abbreviations

AE: adverse event; AESI: AE of special interest; BID: twice daily; CBC: complete blood count; 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; 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; 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; TUC: tucatinib; UC: urothelial cancer

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