SGNTUC-019: PHASE 2 BASKET STUDY OF TUCATINIB AND TRASTUZUMAB IN PREVIOUSLY TREATED SOLID TUMORS WITH HER2 ALTERATIONS (TRIAL IN PROGRESS)

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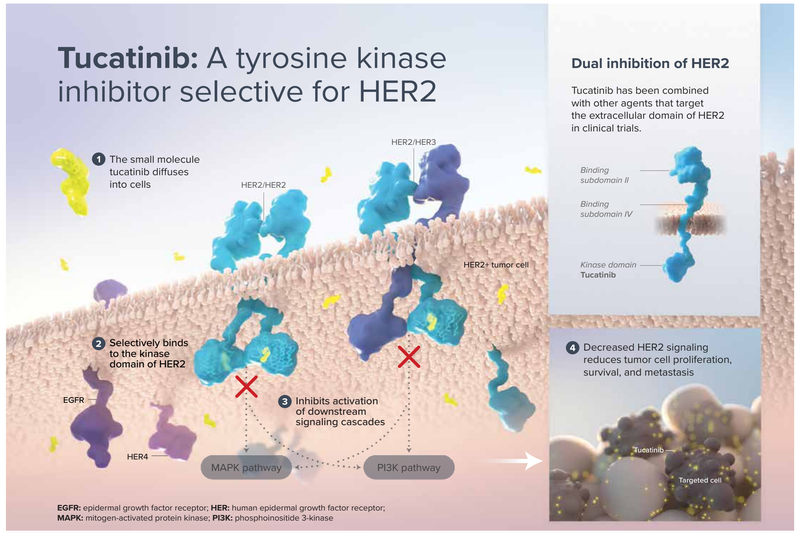
Background

- Tucatinib (TUC) is a highly selective HER2-directed tyrosine kinase inhibitor with minimal EGFR inhibition
- TUC is approved for use in combination with trastuzumab (Tras) and capecitabine in patients with breast cancer with and without brain metastases who have received one or more prior anti-HER2–based regimens in the metastatic setting, based on a statistically significant and clinically meaningful PFS, OS, and ORR benefit over Tras and capecitabine[1]
- Tucatinib is in development as a novel therapy for patients with metastatic CRC and other GI tumors
- In xenograft models of HER2+ and HER2-mutated tumors, dual targeting of HER2 with TUC and Tras showed superior activity to either agent alone
- While various HER2-directed agents have been evaluated in HER2+ and HER2-mutated tumors, HER2-directed therapies have only been approved in breast and gastric cancers.
- The SGNTUC-019 basket study is evaluating TUC combined with Tras in patients with HER2+ or HER2-mutated locally-advanced unresectable or metastatic solid tumors

Tucatinib Proposed Mechanism of Action



Tucatinib is an investigational 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.

Abbreviations: 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: endothelial growth factor receptor; EOT: end of treatment; EQ-5D-5L: European Quality of Life 5-Dimension 5-Level; GEC: gastric or gastroesophageal junction adenocarcinoma; 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; HR+: hormone receptor-positive; HRQoL: health-related quality of life; IHC: immunohistochemistry; IM: intramuscular; 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; PD: progressive disease; PK: pharmacokinetics; PFS: progression-free survival; PO: orally; PPoS: predicted probability of success; PR: partial response; PRO: patient-reported outcomes; q: every; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SMC: safety monitoring committee; TKI: tyrosine kinase inhibitor; Tras: trastuzumab; TUC: tucatinib.

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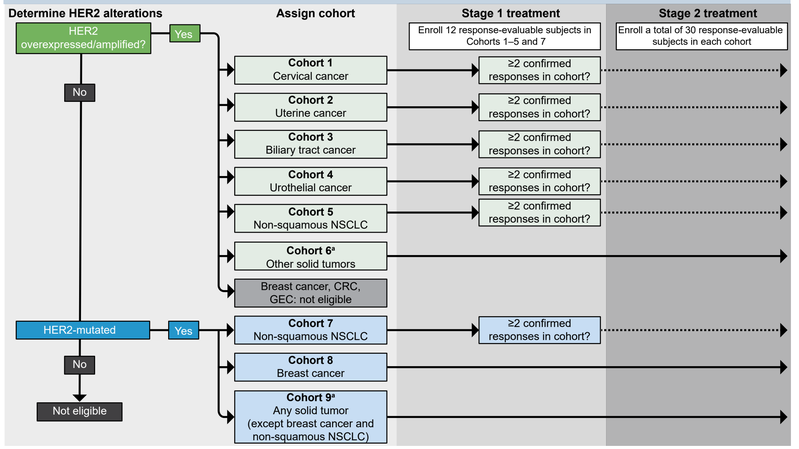
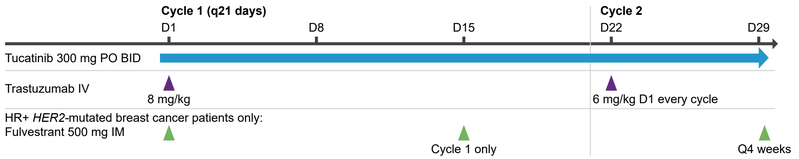
Study Design



a. If a sufficient number of patients with a particular tumor type are enrolled in Cohorts 6 or 9, the sponsor may evaluate that tumor type in a separate cohort, drawn from optional Cohorts 10 to 15.

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 HR+ breast cancer will also receive fulvestrant 500 mg IM once every 4 weeks and on Cycle 1 Day 15



Objectives

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 with or without fulvestrant	• 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

Eligibility

Key Inclusion Criteria

- Histologically or cytologically confirmed, locally-advanced unresectable or metastatic, HER2+ or HER2-mutated solid tumors, including primary brain tumors
- Patients with HER2-negative, HER2-mutant breast cancer: PD on or after ≥1 prior line for advanced disease (chemo-, endocrine, or targeted therapy)
  - Patients with metastatic HR+ disease must have received a prior CDK4/6 inhibitor in the metastatic setting
- Biliary tract cancer: PD on or after ≥1 prior line (chemo-, endocrine, or targeted therapy)
- Non-squamous NSCLC: relapsed/refractory to standard treatment or no standard treatment available
- Cervical cancer: PD on or after ≥1 prior line of systemic therapy (including platinum-based chemotherapy ± bevacizumab in the metastatic setting)
- Other disease types: PD on or after the most recent systemic therapy for advanced disease
- 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 (eligible mutations listed in protocol)
- 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 coagulation function, and LVEF ≥50%

Key Exclusion Criteria

- HER2+ breast cancer, CRC, or gastric or gastroesophageal junction adenocarcinoma
- 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 or chronic liver disease
- Active CNS lesions >2cm (additional exclusion criteria in the protocol)

Assessments

- Disease assessments per RECIST v1.1: q6 weeks for 24 weeks, then q12 weeks. Patients with breast or lung cancer will undergo baseline brain MRI
- Safety assessments: AEs, SAEs, AESIs, treatment modifications, laboratory assessments, 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

Summary

- 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
- The study is open and enrolling, with an estimated study end date of first quarter of 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

1. Murthy RK, et al, N Engl J Med 2020;382:597-609
2. Lee JJ, Liu DD, Clin Trials. 2008; 5(2):93-106

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