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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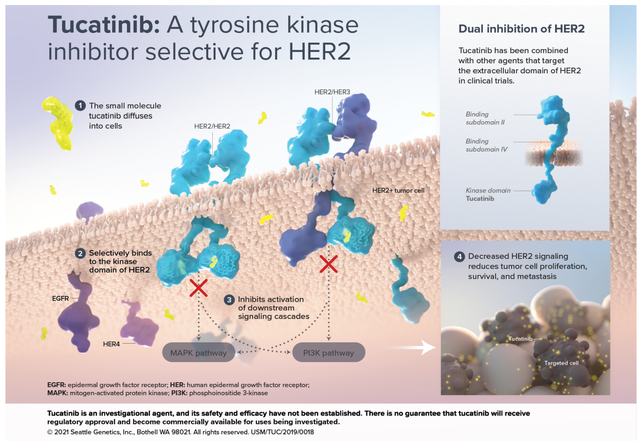
Background

- Tucatinib, a highly selective HER2-directed TK with minimal EGFR inhibition, is approved in combination with trastuzumab and capecitabine in the US, Europe, and other countries for HER2 overexpressed/amplified (HER2+) metastatic breast cancer[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 tucatinib and trastuzumab showed superior activity to either agent alone[2,3].
- While various HER2-directed agents have been evaluated in HER2+ and HER2-mutated tumors, there are no approved HER2-directed therapies outside of breast and gastric cancers.
- The SGNTUC-019 basket study is investigating tucatinib and trastuzumab in patients with HER2+ or HER2-mutated locally-advanced unresectable or metastatic solid tumors.

Tucatinib Proposed Mechanism of Action[4]

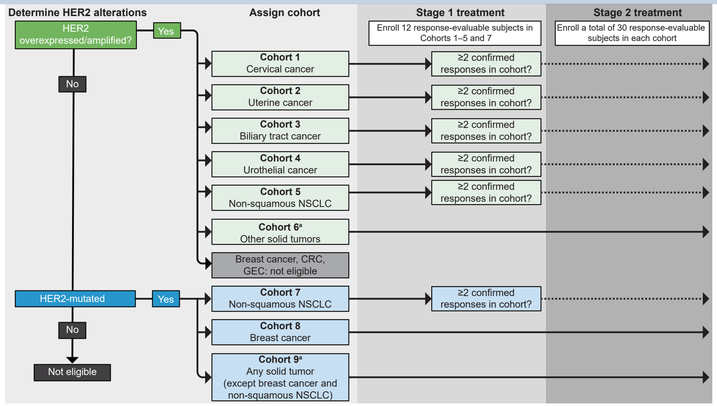


Study Design

- Nine cohorts will enroll patients with either HER2+ or HER2-mutant disease
- 12 response-evaluable patients will initially be enrolled in Stage 1 of the HER2+ cervical, uterine, urothelial, and biliary tract cancers, and HER2+ and HER2-mutated non-squamous NSCLC cohorts
  - If ≥2 responses are observed in a cohort, the posterior probability, according to the PPoS method[5] is >80% that the ORR exceeds 15%.
  - Stage 2 will be opened for that cohort and a total of 30 response-evaluable patients enrolled
- 30 response-evaluable patients will be enrolled in each of the HER2-mutant breast cancer, other HER2+ solid tumors, and other HER2-mutated solid tumors cohorts
- Other HER2+ or HER2-mutant disease-specific cohorts may be opened if enrollment is sufficient

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); D: day; DOR: duration of response; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; EGFR: endothelial growth factor receptor; 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; HR+: hormone receptor-positive; 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; 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; PFS: progression-free survival; PK: pharmacokinetics; 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.

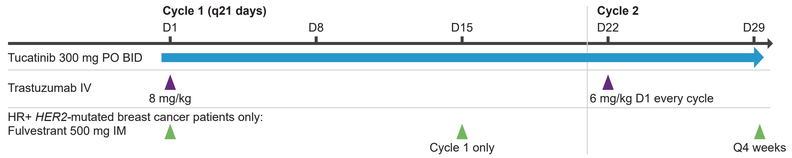
Study Schema



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 tucatinib 300 mg PO BID and trastuzumab 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 tucatinib combined 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 tucatinib combined with trastuzumab 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
To evaluate the PK of tucatinib	Plasma concentrations of tucatinib
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 tucatinib	Identify tumor-specific alterations that are associated with resistance to tucatinib
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
- Prior therapy:
  - Patients with non-squamous NSCLC: Must have progressed during or after standard treatment or for which no standard treatment is available
  - Patients with other disease types: Must have progressed during or after ≥1 prior line of systemic therapy for locally advanced unresectable or metastatic disease
    - » Patients with metastatic HR+ HER2-mutated breast cancer must have received a prior CDK4/6 inhibitor in the metastatic setting
    - » Patients with metastatic cervical cancer must have received platinum-based chemotherapy with or without bevacizumab in the metastatic setting
- Progression during or after, or intolerance of, the most recent line of systemic therapy
- HER2 alterations demonstrated by:
  - HER2+ in tumor tissue by pre-study IHC (3+) or 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 (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, and hematologic, 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 or HER2-mutated gastric or gastroesophageal junction adenocarcinoma without HER2-overexpression/amplification 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 >2 cm unless approved by medical monitor (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 have a baseline brain MRI
  - After discontinuation, assessments continue until disease progression, withdrawal of consent, death, lost 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
- 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 tucatinib in combination with trastuzumab in previously treated patients with HER2 overexpressed/amplified or HER2-mutated solid tumors
- Approximately 75 sites are planned for the US, Asia-Pacific, the EU, and the UK. The study is open and enrolling in all regions.

References

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