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

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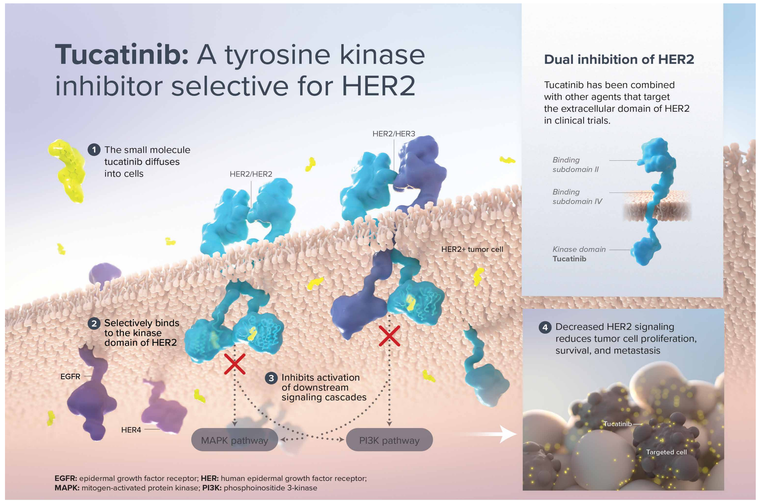
Background

- Tucatinib (TUC) is a highly selective HER2-directed tyrosine kinase inhibitor with minimal EGFR inhibition, approved in multiple regions in combination with trastuzumab (Tras) and capecitabine for HER2+ metastatic breast cancer
- TUC is being developed as a novel therapy for patients with HER2+ metastatic CRC and other GI tumors
- In HER2+ and HER2-mutated xenograft models, dual targeting of HER2 with the combination of TUC and Tras showed superior activity compared to either agent alone[1,2]
- The prognosis for patients with biliary tract cancers (BTCs) remains poor, and the treatment options for these patients are limited
- Given that 12% to 15% of BTCs are HER2+[3] and 1% to 8% of BTCs have HER2 mutations[4], TUC in combination with Tras warrants further evaluation in this patient population
- The SGNTUC-019 basket study (NCT04579380) is evaluating TUC in combination with Tras in patients with HER2+ or HER2-mutated solid tumors, including a cohort of patients with locally advanced unresectable or metastatic BTCs

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.

Study Design

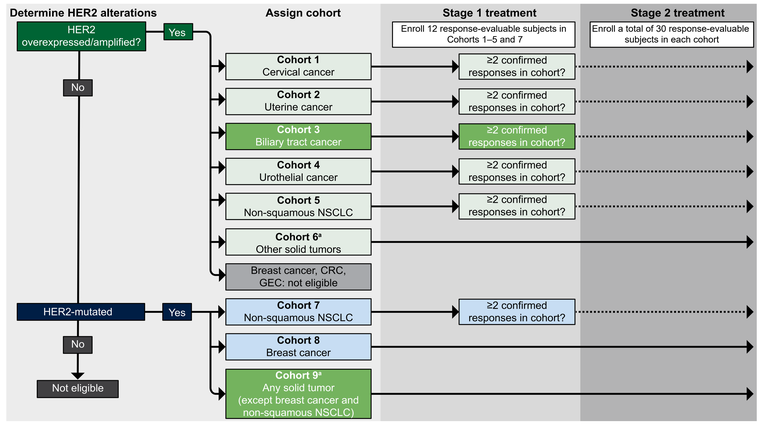
BTC Cohort

- In Stage 1, 12 response-evaluable patients with HER2+ BTC will be enrolled in Cohort 3
  - If ≥2 responses are observed, Cohort 3 will be expanded so that a total of 30 response-evaluable patients with HER2+ BTCs will be evaluated (Stage 2 expansion)
- Patients with HER2-mutated BTC will be enrolled in Cohort 9

Abbreviations

AE: adverse event; AESI: AE of special interest; BID: twice daily; BTC: biliary tract cancer; 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: estimated glomerular filtration rate; 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; 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; 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; Tras: trastuzumab; TUC: tucatinib

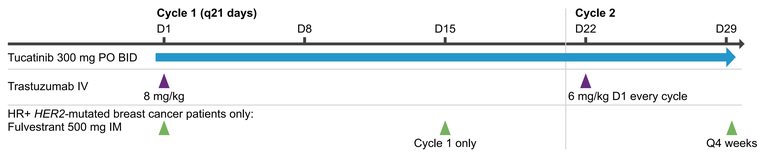
Study Schema



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. Cohort 9 is intended to include HER2-mutated BTC.

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



Objectives

Primary Objective	Endpoints
To evaluate the antitumor activity of TUC in combination 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 in combination with Tras (and with fulvestrant in HR+ HER2-mutated breast cancer)	• 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 identify tumor-specific 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, as assessed by the EQ-5D-5L

Eligibility

Key Inclusion Criteria

- Histologically or cytologically confirmed, locally-advanced unresectable or metastatic, HER2+ or HER-mutated solid tumors, including primary brain tumors
- Patients with BTC must have progressed on or after ≥1 previous line of treatment
- 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, and hematological functions 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 Tras
- 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 the medical monitor

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. Patients in the breast and lung cancer cohorts will undergo baseline brain MRI
- 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 evaluating TUC in combination with Tras in previously treated patients with HER2+ or HER2-mutated solid tumors, including a cohort of patients with locally advanced or metastatic BTC
- Approximately 75 sites are planned in the US, Asia-Pacific, and Europe. All regions are currently enrolling

References

1. Kulukian A et al, Mol Cancer Ther. 2020 Apr;19(4):976-987
2. Peterson S et al, AACR. 2020; Abstract 4222
3. Jovle et al. Journal of Hematology and Oncology. 2015; 8:58
4. Mondaca et al. JCO Precis Oncology. 2019; 17;3:PO.19.00223

Disclosures

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