SGNTUC-019: PHASE 2 BASKET STUDY OF TUCATINIB AND TRASTUZUMAB IN PREVIOUSLY TREATED SOLID TUMORS WITH HER2 ALTERATIONS: *HER2*-MUTATED BREAST CANCER COHORT (ONGOING CLINICAL TRIAL)

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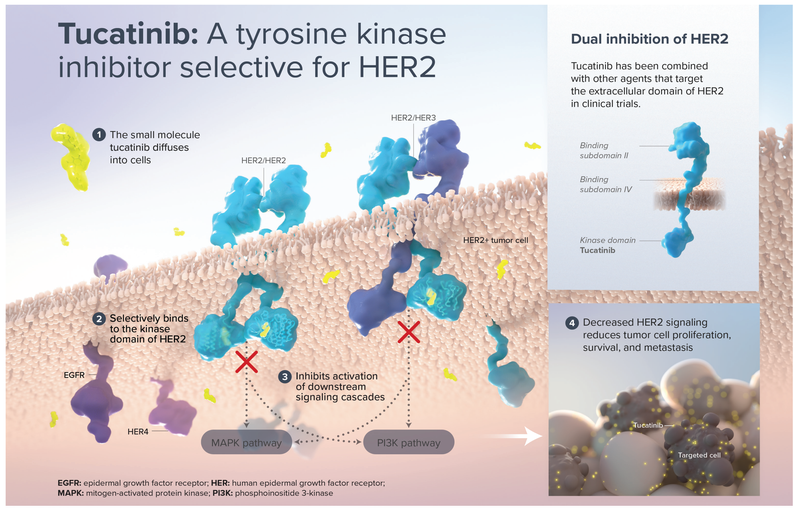
Background

- Tucatinib (TUC), approved in multiple regions in combination with trastuzumab and capecitabine for HER2+ metastatic breast cancer, is a highly selective HER2-directed tyrosine kinase inhibitor with minimal EGFR inhibition
- Tucatinib is also being investigated as a novel therapy for patients with metastatic colorectal cancer and other GI tumors
- *HER2* mutations are present in 2%–5% of primary breast cancer cases, rising to 9% in metastatic breast cancer[1]
- *HER2* mutations lead to enhanced tyrosine kinase activity and tumorigenesis in preclinical models and have been postulated as a mechanism of endocrine therapy resistance[2,3]
- Breast cancer patients with activating HER2 mutations without HER2 overexpression/amplification are not candidates for HER2-targeted therapies under current standard of care, but evidence exists that HER2-mutated disease is a separate genomic subtype of breast cancer and potentially a target for HER2-directed therapy[1]
- 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 breast cancer that is *HER2*-mutated and not HER2 overexpressed/amplified

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

HER2-mutated Breast Cancer Cohort

- The breast cancer cohort will enroll 30 response-evaluable patients with *HER2*-mutated disease
- Patients with HER2+ (overexpression/amplification) breast cancer will not be enrolled

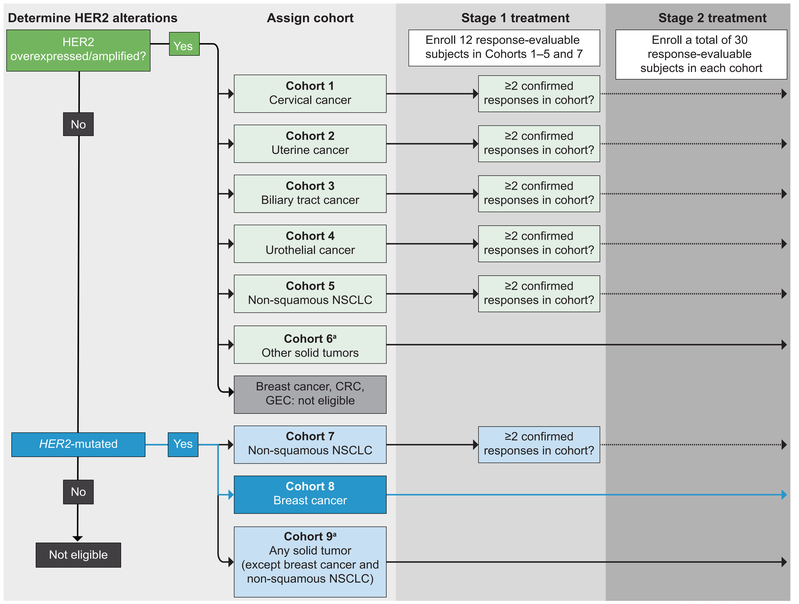
References

1. Yi Z et al, NPJ Breast Cancer. 2020; 6:59
2. Ma et al, Clin Cancer Res. 2017; 23:5687-5695
3. Razavi et al, Cancer Cell. 2018; 34:427-438

Abbreviations

AE: adverse event; AESI: AE of special interest; BID: twice daily; CBC: complete blood count; CDK4/6: cyclin-depend kinases 4/6; 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: epidermal growth factor receptor; EOT: end of treatment; EQ-5D-5L: European Quality of Life 5-Dimension 5-Level; GI: gastrointestinal; GEC: gastroesophageal cancer; 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; MRI: magnetic resonance imaging; 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; q: every; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SMC: safety monitoring committee; TKI: tyrosine kinase inhibitor; TUC: tucatinib

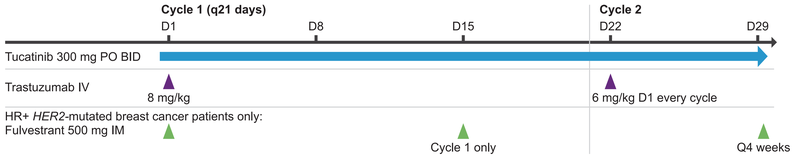
Study Schema



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, optional cohort.

Study Treatment

- Patients will receive TUC 300 mg PO BID and trastuzumab 8 mg/kg IV on Cycle 1 Day 1 then 6 mg/kg every 21 days
- 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



Objectives

Primary Objective	Endpoints
To evaluate the antitumor activity of TUC in combination with trastuzumab with or without fulvestrant	**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 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 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 for Basket Study

Key Inclusion Criteria

- Histologically or cytologically confirmed, locally advanced unresectable or metastatic, HER2+ or *HER2*-mutated solid tumors, including primary brain tumors
- Patients with breast cancer:
  - Must have *HER2*-mutated disease which does not display HER2 overexpression/amplification
  - Must have progressed on or after ≥1 prior line of treatment (chemotherapy, endocrine therapy, or targeted therapy) for locally-advanced unresectable or metastatic breast cancer
  - Patients with metastatic HR+ *HER2*-mutated disease must have received a prior CDK4/6 inhibitor in the metastatic setting
- Disease progression during or after, or intolerance of, the most recent line of systemic therapy
- HER2 alterations demonstrated by
  - HER2 overexpression (3+ IHC) (The breast cancer cohort is only for mutations)
  - *HER2* amplification in tumor tissue by pre-study 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
- Patients with brain metastases may be eligible. Patients in the breast and lung cancer cohorts will undergo baseline brain MRIs
- 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, colorectal cancer, or gastric or gastroesophageal junction adenocarcinoma
- Previous HER2-directed therapy
  - Patients with uterine serous carcinoma or *HER2*-mutated GEC without HER2 overexpression/amplification may have previously received trastuzumab
- Myocardial infarction or unstable angina within 6 months or other clinically significant cardiopulmonary disease
- Known active HBV, HCV, or HIV infection or chronic liver disease
- CNS lesions characterized by
  - Untreated brain lesions >2.0 cm unless approved by medical monitor
  - Ongoing use of systemic corticosteroids (total daily dose of >2 mg dexamethasone or equivalent) for symptoms of brain lesions
  - Brain lesion thought to require immediate local therapy
  - Known or suspected leptomeningeal disease
  - Generalized/complex partial seizures (>1/week) or neurological progression despite CNS-directed therapy

Assessments

- Disease assessments per RECIST v1.1: every 6 weeks for 24 weeks, then every 12 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), 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 on Cycle 1 and Cycle 2 then every 2 cycles during study treatment

Study Status

- Approximately 75 sites are planned in North America, Asia-Pacific, and Europe
- All regions are enrolling

Disclosures

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