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


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Background and Rationale

- Tucatinib (TUC) is a highly selective HER2-directed TKI currently approved for HER2-overexpressed/amplified (HER2+) metastatic breast cancer, on the basis of a statistically significant and clinically meaningful PSFS, OS, and ORR benefit for the addition of TUC to trastuzumab (Tras) and capecitabine
- Tucatinib is in development as a novel therapy for patients with 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
- HER2 mutations are present in 2%-5% of breast cancer cases, rising to 9% in metastatic breast cancer
- Breast cancer patients with activating HER2 mutations without HER2 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

Tucatinib Proposed Mechanism of Action

Tucatinib: A tyrosine kinase inhibitor selective for HER2

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 hormone receptor-positive HER2-mutated breast cancer will also receive fulvestrant 500 mg IM once every 4 weeks and on Cycle 1 Day 15

Study Schema

Her2+ Breast Cancer Cohort

- 30 response-evaluable patients with HER2-mutated locally-advanced unresectable or metastatic breast cancer will be enrolled in Cohort 8

Objectives and Endpoints

Primary Objective

- To evaluate the antitumor activity of TUC combined with Tras with or without fulvestrant

Secondary Objective

- To evaluate the safety and tolerability of TUC combined with Tras with or without fulvestrant

Exploratory Objectives

- To evaluate the PK of TUC
- To explore correlations between HER2 biomarkers and clinical outcomes
- To evaluate PROs

Key Inclusion Criteria

- Histologically or cytologically confirmed, locally-advanced unresectable or metastatic HER2+ or HER2-mutated solid tumors
- Patients with breast cancer:
  - Must have HER2-mutated disease which does not display HER2 overexpression/amplification
  - Must have progressed on or after 2 or 3 prior lines of therapy (chemotherapy, hormone therapy, or targeted therapy) for locally-advanced unresectable or metastatic breast cancer
- Patients with metastatic HER2+ breast cancer disease must have received a prior CDK4/6 inhibitor in the metastatic setting
- Other disease types: Disease progression on or after the most recent systemic therapy for advanced disease (specific eligibility criteria apply for biliary tract and cervical cancer, and NSCLC)
- HER2 alterations demonstrated by:
  - HER2+ in tumor tissue by pre-study IHC/ISH (HC 2 or high ratio 2.0 or gene copy number >8), or
  - HER2 amplification or activating mutations in a pre-study or on-study NGS assay of ctDNA or pre-study tissue NGS assay (eligibility 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

- Breast HER2+ 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. After 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 SMG will monitor safety at regular intervals
- PK assessments in all patients: Tucatinib concentrations on Cycles 2-6 Day 1 and peak concentrations on Cycles 3 Day 1
- Exploratory biomarker assessments: HER2 status by NGS of ctDNA and tissue IHC/ISH and NGS assays
- EO-5d-SL questionnaires are administered every 2 cycles during study treatment

Study Status

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


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