SGNTUC-019 PHASE 2 BASKET STUDY OF TUCATINIB AND TRASTUZUMAB IN SOLID TUMORS WITH HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 ALTERATIONS: UTERINE AND CERVICAL CANCER COHORTS

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BACKGROUND AND RATIONALE
- Tucatinib (TUC) is a highly selective HER2-directed TKI recently approved in multiple regions for HER2 overexpressed/amplified (HER2+) metastatic breast cancer.
- In HER2+ and HER2-mutated xenograft models, dual targeting of HER2 with the combination of TUC and trastuzumab (Tras) showed superior activity compared to either agent alone.
- The prognoses of advanced cervical and uterine cancers are poor, with 5-year overall survival rates for metastatic diseases of 16% and 9%, respectively.
- HER2 overexpression and amplification occur in 21% and 0.5%–14% of cases for cervical cancer, and 18%–80% and 4%–59% of cases for uterine cancers, respectively.
- The SGNTUC-019 basket study (NCT04579380) is evaluating TUC in combination with Tras in patients with HER2+ or HER2-mutated solid tumors, including cohorts of patients with HER2+ cervical or uterine cancers.

TUCATINIB PROPOSED MECHANISM OF ACTION

STUDY DESIGN

Cervical and Uterine Cancer Cohorts
- In Stage I, 12 response-eligible patients will be enrolled in both Cohorts 1 and 2 with HER2+ cervical and uterine cancers.
- Stage 2 will be opened for both Cohorts 1 and 2 to enroll 30 response-eligible patients in each cohort if 22 responses are observed in either cohort in Stage I.
- According to the PPS method, having 22 responders in each cohort means it is likely the ORR exceeds 15%.
- Patients with HER2-mutated cervical and uterine cancers will be enrolled in Cohort 9; specific cohorts may be opened if enrollment is sufficient.

OBJECTIVES

Primary Objective
- To evaluate the antitumor activity of TUC combined with Tras.

Secondary Objectives
- To evaluate the safety and tolerability of TUC combined with Tras (and with fulvestrant in HER2+ metastatic breast cancer).
- To evaluate the PK of TUC.

Exploratory Objectives
- To determine concordance of HER2 alterations as detected by different testing methodologies.
- To identify somatic alterations that are associated with resistance to TUC.
- To evaluate PRRs.

STUDY TREATMENT
- Patients will receive TUC 300 mg PO BID and Tras 8 mg/kg IV on Cycle 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 Day 1 Day 15.

STUDY SCHEMA

ELIGIBILITY

Key Inclusion Criteria
- Histologically or cytologically confirmed, locally-advanced unresectable or metastatic, HER2+ or HER2-mutated solid tumors, including primary brain tumors.
- Must have progressed during or after ≥1 prior line of systemic therapy for locally advanced unresectable or metastatic disease.
- 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 one of the following:
  - HER2 overexpression (≥3+)
  - HER2 amplification in tumor tissue by pre-study IHC (signal ratio ≥2.0 or gene copy number >6)
  - HER2 amplification or activating mutations in a pre-study or on-study NGS assay of ctDNA or pre-study tissue NGS assay.
- ≥18 years of age.
- 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 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 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.
- Safety assessments: AE, SAE, AEs of special interest, treatment modifications, laboratory assessments (metabolic panel, CBC with differential, and EFGR), 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 1–2 Day 1 and peak concentrations on Cycle 3 Day 1.
- Exploratory biomarker assessments: HER2 status by NGS of ctDNA and tissue IHC/IISH 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 overexpressed/amplified or HER2-mutated solid tumors, including cohorts of patients with locally-advanced unresectable or metastatic cervical or uterine cancers.
- Approximately 75 sites are planned for the US, Asia-Pacific, and Europe. The study is open and enrolling in all regions.

REFERENCES

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