SGNTUC-019 is a basket study evaluating tucatinib in combination with trastuzumab in previously treated patients with HER2-overexpressed/amplified or HER2-mutated solid tumors, including a cohort of patients with locally advanced unresectable or metastatic urothelial cancer.

### Study Design

**Urothelial Cancer (UC) Cohort**

Patients with HER2+ UC will be enrolled in Cohort 4. If ≥2 responses are observed, the probability of success, according to the PPUS method, is >80% that enrollment is sufficient.

 Patients with HER2+ UC will be enrolled in Cohort 4; a UC-specific cohort may be opened if the ORR exceeds 10%. Stage 2 will be opened and a total of 30 response-evaluable patients with HER2+ UC enrolled.

To evaluate the PK of TUC Plasma concentrations of TUC will be evaluated in blood and/or tumor tissue.

- **Key Inclusion Criteria**
  - HER2-mutated UC will be enrolled in Cohort 9; a UC-specific cohort may be opened if the ORR exceeds 10%. Stage 2 will be opened and a total of 30 response-evaluable patients with HER2+ UC enrolled.

- **Other solid tumors**
  - Similarly, cohorts for HER2+ cervical, uterine, and bilateral tract cancers, and HER2+ and HER2-mutated non-squamous NSCLC will initially enroll 12 patients and be expanded to 30 patients if 2 responses are observed.

- **Patients with HER2+ UC will be enrolled in Cohort 4:** A UC-specific cohort may be opened if enrollment is sufficient.

### Objectives and Endpoints

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

#### Secondary Objective
- To evaluate the safety and tolerability of TUC combined with Trastuzumab.

#### Primary Endpoint
- Confirmed ORR according to RECIST v1.1 per investigator assessment.

#### Secondary Endpoints
- Disease control:
  - PFS per investigator assessment and OS

#### Additional Endpoints
- Exploratory biomarker assessments: HER2 status by NGS of ctDNA and tissue IHC/ISH and NGS assay.

### Study Treatments

**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+ breast cancer will also receive fulvestrant 500 mg IM every 4 weeks and on Cycle 1 Day 15.

- **Study Assessments**
  - Disease assessments per RECIST v1.1: q6 weeks for 24 weeks, then q12 weeks.
  - ECOG performance status 0 or 1.
  - Measurable disease per RECIST v1.1 according to investigator assessment.

- **Eligibility**
  - HER2 alterations demonstrated by:
    - HER2 amplification or activating mutations in a pre-study or on-study NGS assay of ctDNA or pre-study tissue NGS assay.
    - 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.

- **Key Exclusion Criteria**
  - 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.

- **Key Inclusion Criteria**
  - Known active HBV, HCV, or HIV infection.
  - Active CNS lesions or chronic liver disease.

### Study Sites and Completion Dates

- The study is open, and enrolling, with an estimated study end date of Q1 2023. Approximately 75 sites are planned in North America, Asia-Pacific, and Europe. US is enrolling all cohorts and Asia-Pacific regions are planned.

### References

4. Peterson S et al, AACR. 2020; Abstract 4222

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