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PATIENTS • PURPOSE • PROGRESS

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

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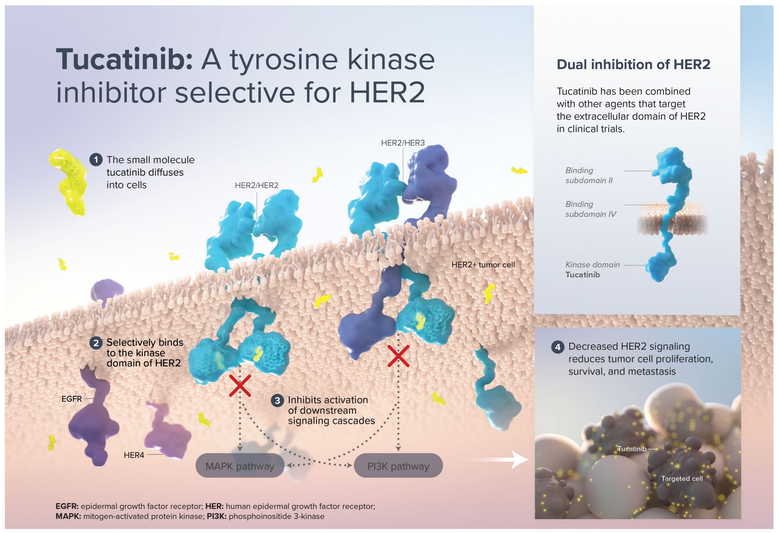
BACKGROUND AND RATIONALE

- Tucatinib (TUC) is a highly selective HER2-directed TKI recently approved in multiple regions for HER2 overexpressed/amplified (HER2+) metastatic breast cancer and in the US for *RAS* WT, HER2+ metastatic colorectal cancer
- In HER2+ and HER2-mutated xenograft models, dual targeting of HER2 with a combination of TUC and trastuzumab (Tras) showed superior activity compared with either agent alone[1,2]
- The prognoses of advanced cervical and uterine cancers are poor, with 5-year relative survival rates for metastatic disease of 17.1% and 18.4%, respectively[3,4]
- HER2 overexpression and amplification occur in approximately 21% and 0.5%–14% of cases for cervical cancer, and in approximately 18%–80% and 4%–69% of cases for uterine cancer, respectively[5]
- 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



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

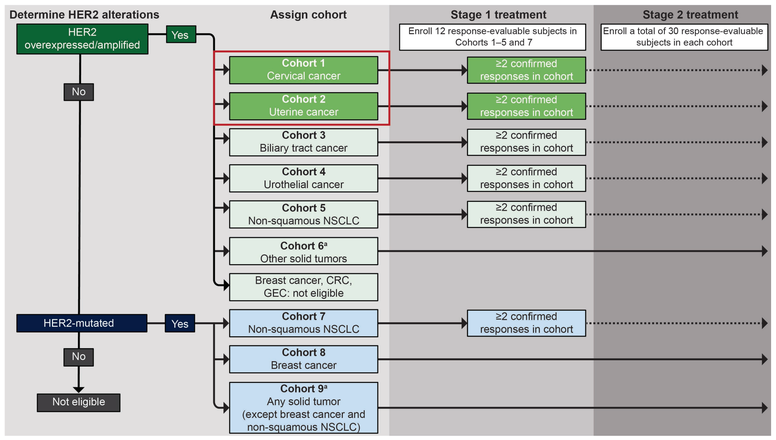
Cervical and Uterine Cancer Cohorts

- In Stage 1, 12 response-evaluable patients will be enrolled in Cohorts 1 and 2, evaluating HER2+ cervical and uterine cancers, respectively
- Stage 2 will be opened for both Cohorts 1 and 2 to enroll 30 response-evaluable patients total in each cohort if ≥2 responses are observed in either cohort in Stage 1
  - According to the PPoS method,[6] having ≥2 responders in each cohort means it is likely the ORR exceeds 15%

STUDY TREATMENT

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

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 cohort, drawn from optional Cohorts 10 to 15.

OBJECTIVES

Primary Objective	Endpoints
To evaluate the antitumor activity of TUC combined with Tras	**Primary endpoint:** Confirmed ORR according to RECIST v1.1 per investigator assessment **Secondary endpoints:** DCR, DOR, PFS per investigator assessment, and OS
Secondary Objective	**Endpoints**
To evaluate the safety and tolerability of TUC combined with Tras	• Type, incidence, severity, and relatedness of AEs and SAEs • Type, 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 assay	Concordance of HER2 alterations as detected by different testing methodologies
To identify tumor-specific alterations that are associated with resistance to TUC	Tumor-specific alterations associated with resistance to TUC
To evaluate PROs	Change from baseline in HRQoL, as assessed by the EQ-5D-5L

REFERENCES

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ABBREVIATIONS

AE, adverse event; AESI, AE of special interest; BID, twice daily; CBC, complete blood count; CNS, central nervous system; CR, complete response; CRC, colorectal cancer; ctDNA, circulating tumor 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; eGFR, estimated glomerular filtration rate; EOT, end of treatment; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level; EU, European Union; GEC, gastric or gastroesophageal junction adenocarcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HER, human epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HER2+, HER2 overexpression or amplification; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; LVEF, left ventricular ejection fraction; MAPK, mitogen-activated protein kinase; 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; PI3K, phosphoinositide 3-kinase; PO, orally; PPoS, predicted probability of success; PR, partial response; PRO, patient-reported outcomes; q, every; *RAS*, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SMC, safety monitoring committee; TKI, tyrosine kinase inhibitor; Tras, trastuzumab; TUC, tucatinib; US, United States; WT, wild-type.

ELIGIBILITY

Key Inclusion Criteria

- Histologically or cytologically confirmed, locally advanced unresectable or metastatic, HER2+ or HER2-mutated solid tumors, including primary brain tumors
- Progression 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 overexpression/amplification demonstrated by one of the following:
  - HER2 overexpression (3+ IHC)
  - HER2 amplification in tumor tissue by pre-study ISH (signal ratio ≥2.0 or gene copy number >6)
  - HER2 amplification in a pre-study or on-study NGS assay of ctDNA or pre-study tissue NGS assay
- ≥18 years of age
- ECOG performance status of 0 or 1
- 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: 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 overexpressed/amplified or HER2-mutated solid tumors, including cohorts of patients with locally advanced unresectable or metastatic HER2+ cervical or uterine cancer
- Enrollment is currently open at 64 sites in the US, EU, and Asia Pacific regions

DISCLOSURES

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