Tucatinib: a highly selective HER2-directed TKI with minimal EGFR inhibition, is approved in combination with trastuzumab and capecitabine in the US, Europe, and other countries for advanced HER2-overexpressed/amplified or HER2+ metastatic breast cancer1,2.

Tucatinib is in development as a novel therapy for patients with metastatic CRC and other GI solid tumors. In xenograft models of HER2+ and HER2-mutated tumors, dual targeting of HER2 with tucatinib and trastuzumab showed superior activity to either agent alone3,4. While various HER2-directed agents have been evaluated in HER2+ and HER2-mutated tumors, there are no approved HER2-directed therapies outside of breast and gastric cancers. The SGNTUC-019 basket study is investigating tucatinib and trastuzumab in patients with HER2+ or HER2-mutated locally-advanced unresectable or metastatic solid tumors.

### Study Design

- **Objectives**
  - To identify somatic alterations that are associated with resistance to tucatinib.
  - To determine concordance of HER2 alterations by tissue and blood assays.
  - To evaluate the PK of tucatinib.
  - Secondary Objectives
    - To evaluate the safety and tolerability of tucatinib combined with trastuzumab with or without fulvestrant.
    - Secondary Objectives
      - Incidence, severity, and relatedness of AEs and SAEs
      - Incidence and incidence of laboratory abnormalities
      - Frequency of dose modifications due to AEs
      - Other relevant safety variables including MBRs

- **Key Inclusion Criteria**
  - Histologically or cytologically confirmed, locally-advanced HER2-overexpressed or metastatic, HER2+ or HER2-mutated solid tumors, including primary brain tumors.
  - Prior therapy:
    - Patients with non-squamous NSCLC: Must have progressed on or after standard treatment for which no standard treatment is available.
    - Patients with other disease other than brain: Must have progressed during or after prior line of systemic therapy for loco-regionally advanced 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:
    - HER2+ in tumor tissue by pre-study IHC (3+) or 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 (eligible mutations listed in protocol).

- **Assessments**
  - Disease assessments per RECIST v1.1: q6 weeks for 24 weeks, then q12 weeks.
  - Patients with breast or lung cancer will have a baseline brain MRI.
  - Adverse events assessment continues until disease progression, withdrawal of consent, death, lost to follow-up, or study closure.
  - Safety assessments: AEs, SAEs, AEiTs, treatment modifications, laboratory assessments (metabolic panel, CBC with differential, and eGFR), vital signs, LVEF at baseline and EOT. An SMC will monitor safety at regular intervals.
  - PK assessments in all patients. Trough tucatinib concentrations on Cycles 2–6 Day 1 and peak concentrations on Cycle 3 Day 1.
  - Biomarker assessments: HER2 status by NGS of ctDNA and tissue IHC/ISH and NGS assays.
  - EQ-SD-5L questionnaires are administered every 2 cycles during study treatment.

### Summary

- **Eligibility**
  - Measurable disease per RECIST v1.1 according to investigator assessment.
  - ECOG performance status 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 trastuzumab.
  - Mucosal inflammatory or unstable anemia within 6 months, or clinically significant carcinoid tumor.
  - Known active HIV, HCV, or HIV infection or chronic liver disease.
  - Active CNS lesions ≥2 cm unless approved by medical monitor.

- **References**
  3. Martin Reck, m.reck@lungenclinic.de

### Abbreviations

- AE: adverse event
- AESI: AE of special interest
- BID: twice daily
- CBC: complete blood count
- CNS: central nervous system
- CRC: colorectal cancer
- CT: computed tomography
- D5/LD: day 5/life day
- DLQI: Dermatology Life Quality Index
- DNA: deoxyribonucleic acid
- ECOG: Eastern Cooperative Oncology Group
- eGFR: estimated glomerular filtration rate
- EORTC: European Organisation for Research and Treatment of Cancer
- GI: gastrointestinal
- GIIN: Global Initiative on Inoperable NSCLC
- IHC: immunohistochemistry
- ISH: in situ hybridization
- IV: intravenous
- LVEF: left ventricular ejection fraction
- MRI: magnetic resonance imaging
- NBR: hormone receptor-negative
- NGS: next-generation sequencing
- NSCLC: non-small cell lung cancer
- ORR: objective response rate
- OSI: overall survival
- PD: progressive disease
- PET: positron emission tomography
- PR: partial response
- PRO: patient-reported outcomes
- PFS: progression-free survival
- RECIST: Response Evaluation Criteria in Solid Tumors
- SAE: serious adverse event
- SAEI: SAE of special interest
- SE: survival extension
- SMC: safety monitoring committee
- TKI: tyrosine kinase inhibitor
- WHO: World Health Organization
- X: any value
- Y: any value greater than X
- Z: any value less than Y

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