Tucatinib Proposed Mechanism of Action


dual inhibition of HER2 and Tras, which leads to reduced tumor cell proliferation, reduced tumor cell survival, and reduced metastasis.

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

Background
• Tucatinib (TUC) is a highly selective HER2-directed tyrosine kinase inhibitor with minimal EGFR inhibition
• TUC is approved for use in combination with trastuzumab (Tras) and capecitabine in patients with breast cancer with and without metastases who have received one or more prior anti-HER2-based regimens in the metastatic setting, based on a statistically significant and clinically meaningful PFS, OS, and OBR benefit over Tras and capecitabine
• TUC is in development as a novel therapy for patients with metastatic CRC and other GI tumors, HER2-directed therapies have only been approved in breast and gastric cancers

Study Design

- Patients will receive TUC 300 mg PO BID and Tras 8 mg/kg IV on Cycle 1 Day 1 and 6 mg/kg on Cycle 1 Day 15
- ECOG performance status 0 or 1
- HER2 alterations demonstrated by:
  - IHC: immunohistochemistry
  - ISH: in situ hybridization
  - IV: intravenous

Eligibility

Key Inclusion Criteria
• Historical and/or cytologically confirmed, locally-advanced unresectable or metastatic, HER2+ or HER2-mutated solid tumors, including primary brain tumors
• Patients with HER2-negative, HER2-mutant breast cancer: PD on or after ≥1 prior line for advanced disease (chemo-, endocrine, or targeted therapy)
• Patients with metastatic HR+ disease must have received a prior CDK4/6 inhibitor in the metastatic setting
• Bilary tract cancer: PD on or after ≥1 prior line (chemo-, endocrine, or targeted therapy)
• Non-squamous NSCLC: relapsed/refractory to standard treatment or no standard treatment available
• Cervical cancer: PD on or after ≥1 prior line of systemic therapy (including platinum-based chemotherapy a bevacizumab in the metastatic setting)
• Other disease types: PD on or after the most recent systemic therapy for advanced disease
• HER2 alterations demonstrated by:
  - HER2 in tumor tissue
  - Pre-CYp 1/2 and H/CySH (H/Cy signals 320 or gene copy number ≥4), or HER2 amplification or activating mutations in a pre-CYp or H/CySH assay (eligible mutations listed in protocol)
• Measurable disease per RECIST v1.1 according to investigator assessment
• ≥18 years of age
• Adequate hepatic, renal, hematologic, and coagulation function, 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 may have received prior trastuzumab
• Myocardial infarction or unstable angina within 6 months, or clinically significant cardiopulmonary disease
• Known active HJV, HCV, or HIV infection or chronic liver disease
• Active CNS lesions >2mm (additional exclusion criteria in the protocol)

Assessments
• Disease assessments per RECIST v1.1: q6 weeks for 24 weeks, then q12 weeks. Patients with breast or lung cancer will undergo baseline brain MRI
• Safety assessments: AES, SAEs, AEs/treatment modifications, laboratory assessments, 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 tucatinib concentrations on Cycle 2 Day 1 every 4 weeks
• EQ-5D-5L questionnaires are administered every 2 cycles during study treatment

References
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