PHASE 1B/2 OPEN-LABEL, DOSE ESCALATION AND EXPANSION TRIAL OF TUCATINIB IN COMBINATION WITH TRASTUZUMAB AND OXALIPLATIN-BASED CHEMOTHERAPY IN PATIENTS WITH UNRESECTABLE OR METASTATIC HER2+ GASTROINTESTINAL CANCERS (TRIAL IN PROGRESS)

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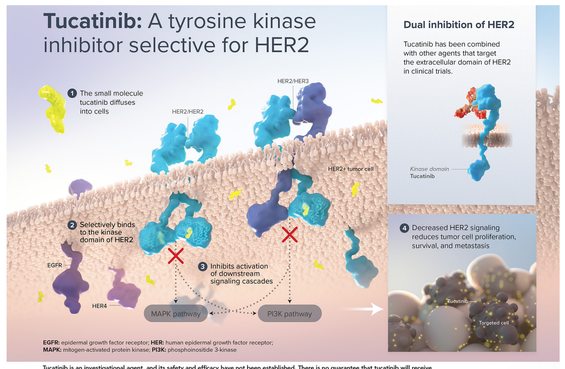
Background and Rationale

- Globally, ~35% of all cancer-related deaths occur from gastrointestinal (GI) cancers;[1] safe and effective treatments for GI cancers include fluoropyrimidines in combination with oxaliplatin.
- Human epidermal growth factor receptor 2 (HER2/ERBB2) gene amplification or overexpression of its protein is observed in ~6% to 30% of gastric, gastroesophageal junction (GEJ), and esophageal cancers,[2] ~3% to 5% of metastatic colorectal cancers,[3, 4] and ~1% to 6% of other GI cancers.[5, 6]
- There is growing interest in HER2-targeting strategies for patients with GI cancers.
  - In the 1st line setting, trastuzumab + oxaliplatin-based chemotherapy is a standard of care for metastatic HER2+ gastric and GEJ adenocarcinomas.
  - In the 3rd line setting, trastuzumab deruxtecan has overall survival benefits and is approved in the United States (US) for treatment of HER2+ gastric and GEJ cancer.
  - Studies evaluating dual HER2 targeting therapies (trastuzumab + pertuzumab[7] or trastuzumab + lapatinib[8, 9]) have also shown activity in HER2+ colorectal cancer.
- Tucatinib is an oral tyrosine kinase inhibitor that is highly selective for HER2, with low affinity for the epidermal growth factor receptor (EGFR).[10, 11]
- Tucatinib has antitumor activity, alone or in combination with trastuzumab, in cell-line and patient-derived xenograft models of GI cancers.[11]
- Tucatinib is approved for HER2+ metastatic breast cancer in the US, Canada, the European Union, and several other countries, and is further being investigated as a novel therapy for patients with HER2+ GI cancers.

Clinical Rationale

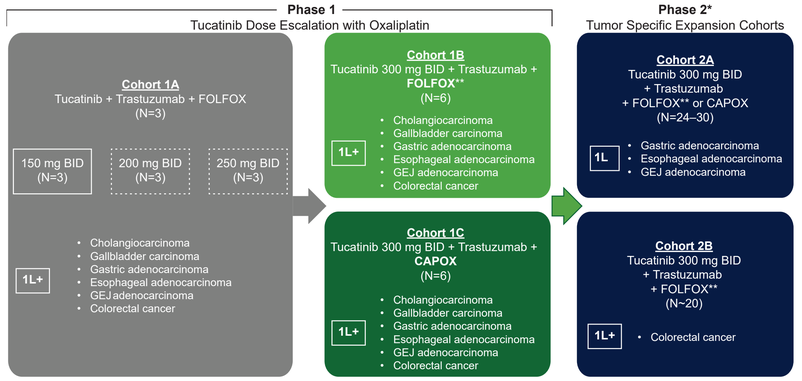
- Despite advances in the treatment of HER2+ GI cancers, there are opportunities to improve on the currently available HER2 directed GI cancer therapies.
- Interim results from the MOUNTAINEER (NCT03043313) study showed promising activity for tucatinib + trastuzumab in HER2+ metastatic colorectal cancer.
  - In 23 response-evaluable patients, an objective response rate of 52.2% (12 partial responses), median duration of response of 10.4 months, median progression-free survival of 8.1 months, and median overall survival of 18.7 months was observed.[12]
- SGNTUC-024 (NCT04430738) is a multicenter, phase 1b/2 dose escalation and expansion study to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy in patients with HER2+ GI cancers.
- SGNTUC-024 will include both tucatinib PK and oxaliplatin PK, in the presence and absence of tucatinib, to evaluate potential drug-drug interactions. Oxaliplatin is a substrate for the multidrug and toxin extrusion (MATE) 1/MATE2-K and organic cation transporters (OCT), which transport oxaliplatin through proximal renal tubular epithelial cells, and tucatinib is an inhibitor of MATE1/MATE2-K and OCT2.

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



*If safety data from the phase 1b cohorts are acceptable, phase 2 cohorts may begin enrollment.
**mFOLFOX6 or mFOLFOX7 can be used, based on investigator discretion.

FOLFOX and Trastuzumab (Q2W)	
Trastuzumab	6 mg/kg IV loading dose on Cycle 1 Day 1 only, then 4 mg/kg IV on Day 1 of each subsequent cycle
Oxaliplatin	85 mg/m^2 IV on Day 1
Leucovorin	Administer concurrent with oxaliplatin as follows: mFOLFOX6: 400 mg/m^2 IV on Day 1; mFOLFOX7: 200 mg/m^2 IV on Day 1
Fluorouracil	mFOLFOX6: 400 mg/m^2 IV bolus on Day 1, then 2400 mg/m^2 IV infusion administered over 46 hours beginning on Day 1
	mFOLFOX7: 2400 mg/m^2 IV infusion administered over 46 hours

CAPOX and Trastuzumab (Q3W)	
Trastuzumab	8 mg/kg IV loading dose on Cycle 1 Day 1 only, then 6 mg/kg IV on Day 1 of each subsequent cycle
Oxaliplatin	130 mg/m^2 IV on Day 1
Capecitabine	1000 mg/m^2 PO BID: Cycle 1 (evening of Day 1 to morning of Day 15); Cycle 2 and thereafter (Days 1 to 14)

FOLFOX=fluorouracil, leucovorin, and oxaliplatin; CAPOX=capecitabine and oxaliplatin

Key Eligibility Criteria

Key Inclusion Criteria

- Histologically confirmed HER2+ GI cancer

Colorectal cancer, cholangiocarcinoma, and gall bladder carcinoma	HER2+ by IHC3+ or FISH/CISH ≥2 or gene copy number >6 or amplification by NGS in tissue or blood
Gastric, GEJ, and esophageal adenocarcinoma	HER2+ by IHC3+ or by IHC2+/ISH+

- Eligible to receive an oxaliplatin-based regimen as part of standard of care
- Phase 1b: measurable or non-measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigator assessment
- Phase 2: measurable disease per RECIST v.1.1 by investigator assessment
- Eastern Cooperative Oncology Group performance status of 0 or 1

Key Exclusion Criteria

- Known hypersensitivity to oxaliplatin, fluoropyrimidines, leucovorin, trastuzumab, or compounds similar to tucatinib (except for ≤ Grade 2 infusion related reactions that were successfully managed)
- Clinically significant cardiopulmonary disease
- Patients in the phase 2 cohorts cannot have received prior anti-HER2 therapies
- Patients with known active central nervous system metastases*

* For Cohorts 2A and 2B, patients with active central nervous system metastases may be enrolled if certain criteria are met.

Study Endpoints

Phase 1b	Phase 2
Primary	
• Incidence of dose-limiting toxicities	• Safety and tolerability (AEs, laboratory abnormalities, other relevant safety variables)
Secondary	
• Safety and tolerability (AEs, laboratory abnormalities, other relevant safety variables) • Change in GFR from baseline through 2 cycles of combination therapy • PK parameters of tucatinib and oxaliplatin	**Cohort 2A** • cORR, DOR, and PFS per RECIST v1.1 by investigator assessment, OS, and PK parameters of tucatinib
Exploratory	
• ORR per RECIST v1.1 by investigator assessment • Biomarkers of response, resistance, or toxicity	**Cohort 2B** • cORR, DOR, and PFS per RECIST v1.1 by investigator assessment, and OS **Cohorts 2A and 2B** • Biomarkers of response, resistance, or toxicity

Study Assessments

Efficacy
- Radiographic disease assessment per RECIST v1.1 by investigator

Safety
- Adverse events, laboratory abnormalities, vital signs, and other relevant safety variables

Pharmacokinetics
- Phase 1b
  - For tucatinib: from Cycle 2 to Cycle 6
  - For oxaliplatin: Cycle 1 and Cycle 2
- Phase 2
  - For tucatinib: from Cycle 2 to Cycle 6

Biomarkers
- Assessment of HER2 status
- Biomarkers of response, resistance, or toxicity

Summary

- SGNTUC-024 is a phase 1b/2 dose escalation and expansion study to determine the recommended dose of tucatinib, and to assess safety, tolerability, and efficacy of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy in patients with HER2+ GI cancers.
- Enrollment is ongoing in the US with up to 25 sites planned.

Abbreviations: 1L=first line; AEs=adverse events; BID=twice a day; CAPOX=capecitabine and oxaliplatin; CISH=chromogenic in situ hybridization; cORR=confirmed objective response rate; DOR=duration of response; EGFR=epidermal growth factor receptor; FISH=fluorescence in situ hybridization; FOLFOX=fluorouracil, leucovorin, and oxaliplatin; GEJ=gastroesophageal junction; GFR=glomerular filtration rate; GI=gastrointestinal; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=in situ hybridization; IV=intravenous; MATE=multidrug and toxin extrusion; NGS=next generation sequencing; OCT=organic cation transporter; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; PO=oral; Q2W=every 2 weeks; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria In Solid Tumors; US=United States.

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