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

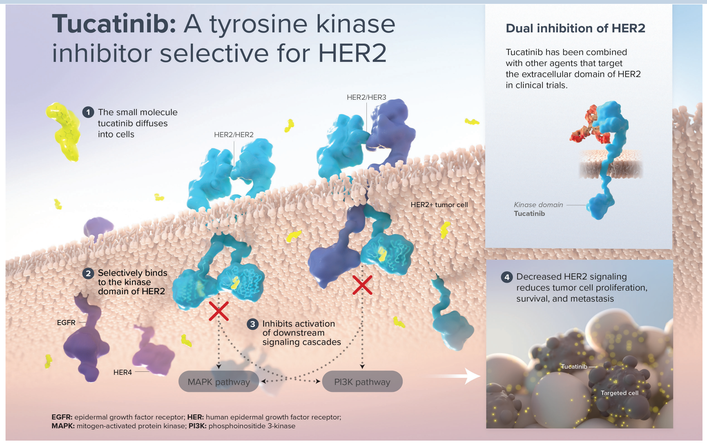
Haeseong Park,[1] Tanios Bekaii-Saab,[2] Sunnie S. Kim,[3] Suneel Kamath,[4] Michael J. Pishvaian,[5] Christopher T. Chen,[6] David B. Zhen,[7] JoAl Mayor,[8] Qianwen Tan,[8] John H. Strickler[9]

[1]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA, [2]Division of Hematology and Oncology, Mayo Clinic, Phoenix, AZ, USA, [3]University of Colorado Cancer Center, Aurora, CO, USA, [4]Cleveland Clinic, Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA, [5]Johns Hopkins Kimmel Cancer Center, Washington, DC, USA, [6]Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA, USA, [7]University of Washington, Seattle, WA, USA, [8]Seagen Inc., Bothell, WA, USA, [9]Duke University Medical Center, Durham, NC, USA

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 CRCs;[3, 4] and ~1% to 6% of other GI cancers.[5, 6]
- HER2-targeting strategies and immune checkpoint inhibitors have demonstrated clinically meaningful outcomes for patients with HER2+ GI cancers.
  - In the 1st-line setting, trastuzumab + chemotherapy is a standard of care for metastatic HER2+ gastric, GEJ, and esophageal adenocarcinomas and is approved in the US for treatment of HER2+ gastric and GEJ cancers.[7]
  - Further, the addition of pembrolizumab to trastuzumab + chemotherapy has demonstrated enhanced response rates in advanced HER2+ gastric and GEJ cancers.[8]
  - In the 3rd-line setting, trastuzumab deruxtecan has an overall survival benefit compared to chemotherapy and is approved in the US for treatment of HER2+ gastric and GEJ cancers.[9]
  - Studies evaluating dual HER2 targeting therapies (trastuzumab + pertuzumab[10] or trastuzumab + lapatinib[11, 12]) have shown activity in HER2+ CRC.
- Tucatinib is a highly selective HER2-directed tyrosine kinase inhibitor with minimal EGFR inhibition,[13, 14] approved in multiple regions for HER2+ metastatic breast cancer.
- In patient-derived xenograft models of HER2+ tumors (including esophageal, gastric, and colorectal cancers), tucatinib + trastuzumab showed superior anti-tumor activity compared with either agent alone.[14]
- In murine tumor models, tucatinib favorably modulated the immune microenvironment and demonstrated enhanced activity in combination with an anti-PD1 inhibitor.[15]
- Despite advances in the treatment of HER2+ GI cancers, there are opportunities to improve on the currently available HER2-directed GI cancer therapies.
- In the MOUNTAINEER (NCT03043313) study, in 23 response-evaluable patients with HER2+ metastatic CRC, an ORR of 52.2% (12 partial responses), a median DOR of 10.4 months, a median PFS of 8.1 months, and a median OS of 18.7 months were observed.[16]

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.

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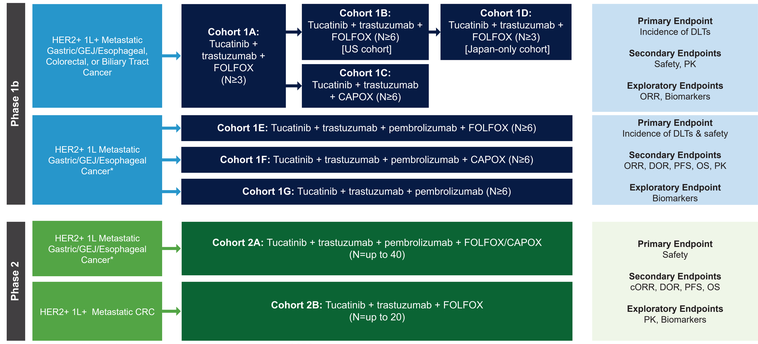
Study Design

- 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 and/or pembrolizumab 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.

Study Design



*Patients may enroll in pembrolizumab-containing cohorts irrespective of CPS.

Tucatinib (BID)

Cohort 1A	All other cohorts
150 mg PO	300 mg PO

Pembrolizumab (Q6W)

Cohorts 1E, 1F, 1G*, and 2A
400 mg IV

* Trastuzumab dosing for Cohort 1G is 8 mg/kg IV loading dose on Cycle 1 Day 1 then 6 mg/kg IV on Day 1 Q3W

FOLFOX (Q2W) and Trastuzumab (Q2W or Q3W)

	Cohorts 1A and 1B	Cohorts 1D, 1E, 2A, and 2B
Trastuzumab	6 mg/kg IV loading dose on Cycle 1 Day 1 then 4 mg/kg IV on Day 1 Q2W	8 mg/kg IV loading dose on Cycle 1 Day 1 then 6 mg/kg IV on Day 1 Q3W
Oxaliplatin	85 mg/m^2 IV on Day 1 Q2W	
Leucovorin	Administer concurrent with oxaliplatin as follows: mFOLFOX6: 400 mg/m^2 IV on Day 1 Q2W	
	mFOLFOX7: 200 mg/m^2 IV on Day 1 Q2W	
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 Q2W	
	mFOLFOX7: 2400 mg/m^2 IV infusion administered over 46 hours Q2W	

CAPOX and Trastuzumab (Q3W)

	Cohorts 1C, 1F, and 2A
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 on Days 1 to 14

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

Key Eligibility Criteria

Key Inclusion Criteria

- Histologically confirmed HER2+ GI cancer

Cancer Type	HER2+ confirmation
Colorectal cancer, cholangiocarcinoma, or 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, or esophageal adenocarcinoma	HER2+ by IHC3+ or by IHC2+/ISH+

- Eligible to receive an oxaliplatin-based regimen as part of standard of care (except Cohort 1G)
- 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 planned study treatment (except for Grade ≤2 infusion related reactions that were successfully managed)
- Clinically significant cardiopulmonary disease
- Cohorts 1E, 1F, 1G, and 2A:
  - Previous chemotherapy for metastatic/unresectable disease
  - Previous therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor and was discontinued from that treatment because of Grade ≥3 immune-related AE
- Phase 2: previous anti-HER2 therapies
- 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.

Key Study Endpoints

Cohorts		Primary	Secondary
Phase 1b	**1A & 1B** (tucatinib dose escalation with trastuzumab and FOLFOX)	• Incidence of renal DLTs	• Safety (AEs, laboratory abnormalities, safety variables) • Change in GFR from baseline through 2 cycles of combination therapy • PK parameters of tucatinib and oxaliplatin
	1C, 1E, 1F, 1G (tucatinib in combinations)	• Safety (AEs, DLTs, laboratory abnormalities)	• ORR, DOR, and PFS per RECIST v1.1 by INV; OS; and PK parameters of tucatinib
	1D (Japanese safety evaluation)	• Safety (AEs, DLTs, laboratory abnormalities); vital signs/safety variables; frequency of dose holds, dose reductions, and discontinuations	
Phase 2	**2A & 2B** (tumor-specific expansion)	• Safety (AEs, DLTs, laboratory abnormalities); vital signs/safety variables	• cORR, DOR, and PFS per RECIST v1.1 by INV; OS

Study Assessments

Efficacy

- Radiographic disease assessment per RECIST v1.1 by investigator

Safety

- AEs, laboratory abnormalities, vital signs, and other relevant safety variables

Pharmacokinetics

- Cohorts 1A and 1B
  - Tucatinib: Cycle 2 to Cycle 6
  - Oxaliplatin: Cycle 1 and Cycle 2
- Cohorts 1C, 1E, 1F, 1G, 2A, and 2B
  - Tucatinib: Cycle 2 to Cycle 6
- Cohort 1D
  - Tucatinib: Cycle 1 to Cycle 6 and EOT

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 and/or pembrolizumab in patients with HER2+ GI cancers.
- The phase 1b portion of the trial is currently enrolling.

Abbreviations

1L=first line; 1L+=first line and later; AEs=adverse events; BID=twice a day; CAPOX=capecitabine and oxaliplatin; CISH=chromogenic in situ hybridization; cORR=confirmed objective response rate; CPS=combined positive score; CRC=colorectal cancer; DLT=dose limiting toxicity; 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/ERBB2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; INV=investigator; 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; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1; PD-L2=programmed cell death ligand 2; PFS=progression-free survival; PK=pharmacokinetics; PO=oral; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; RECIST=Response Evaluation Criteria In Solid Tumors; US=United States.

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