A Global, Randomized, Open-Label, Phase 3 Study of Zanidatamab in Combination With Chemotherapy With or Without Tislelizumab for First-Line Treatment of HER2+ Unresectable Locally Advanced or Metastatic Gastroesophageal Adenocarcinoma (GEA) (HERIZON-GEA-01) – (NCT05152147)

Study Overview

Purpose	To evaluate and compare the efficacy and safety of zanidatamab in combination with chemotherapy with or without tislelizumab vs standard of care (trastuzumab with chemotherapy) as first-line treatment for patients with advanced/metastatic HER2+ GEA
Condition(s)	Unresectable locally advanced, recurrent or metastatic HER2+ GEA (adenocarcinoma of the stomach or esophagus, including the gastroesophageal junction)
Drug(s)	• Trastuzumab plus physician's choice of chemotherapy (CAPOX or FP) , or • Zanidatamab plus physician's choice of chemotherapy (CAPOX or FP) , or • Zanidatamab and tislelizumab plus physician's choice of chemotherapy (CAPOX or FP)
Study Phase	Phase 3
Participating Countries	Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Czechia, Estonia, France, Georgia, Germany, Greece, Guatemala, India, Ireland, Italy, Japan, Republic of Korea, Malaysia, Mexico, Netherlands, Poland, Portugal, Romania, Serbia, Singapore, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, and United Kingdom

Selected Outcome Measures

Primary Outcome Measures:

- PFS by BICR
- OS

Secondary Outcome Measures:

- Confirmed ORR by BICR
- DOR by BICR
- PFS, confirmed ORR, and DOR per Investigator assessment
- Frequency and severity of adverse events or clinical laboratory abnormalities
- Health-related quality of life as assessed by EORTC QLQ-C30, EORTC QLQ-OG25, and EQ-5D-5L
- Serum concentration of zanidatamab, tislelizumab, and trastuzumab
- Pharmacokinetic parameters for zanidatamab and tislelizumab
- Incidence of anti-drug antibodies

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http://www.clinicaltrials.gov
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Key Eligibility Criteria

Key Inclusion Criteria:

- Patients must be ⩾18 years of age
- Patients must have histologically confirmed unresectable locally advanced, recurrent or metastatic HER2+ GEA
- Patients with esophageal adenocarcinoma must not be eligible for combined chemoradiotherapy at the time of enrollment
- Patients must have assessable disease as defined by RECIST v1.1
- Patients must have an ECOG performance status of 0 or 1
- Patients must have adequate organ function and left ventricular ejection fraction ⩾50%

Key Exclusion Criteria:

- Patient has received prior treatment with a HER2-targeted agent
- Patient has received prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
- Patient has received prior treatment with systemic antineoplastic therapy for unresectable locally advanced, recurrent or metastatic GEA
- Patient has untreated CNS metastases, symptomatic CNS metastases, or radiation treatment for CNS metastases within 4 weeks prior to randomization
- Patient has a known history of or ongoing leptomeningeal disease
- Patient has an active infection or concomitant condition that could substantially increase the risk associated with the patient's participation in the study

Treatment Regimen

- **Active comparator Arm A:** Trastuzumab administered IV plus physician's choice of CAPOX or FP
  - CAPOX: Capecitabine is administered orally and oxaliplatin is administered IV
  - FP: 5FU and cisplatin are administered IV
- **Experimental Arm B:** Zanidatamab administered IV plus physician's choice of CAPOX or FP
- **Experimental Arm C:** Zanidatamab administered IV and tislelizumab IV plus physician's choice of CAPOX or FP

5FU = 5-fluorouracil, BICR = blinded independent central review, CAPOX = capecitabine + oxaliplatin, CNS = central nervous system, DOR = duration of response, ECOG = Eastern Cooperative Oncology Group, EORTC QLQ-C30/-OG25 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30/-Esophageal and Gastric module, EQ-5D-5L = EuroQol 5-dimensions 5-levels questionnaire, FP = 5-fluorouracil + cisplatin, GEA = gastroesophageal adenocarcinoma, HER2 = human epidermal growth factor receptor 2, IV = intravenously, ORR = objective response rate, PD-1 = programmed cell death-1, PD-L1/2 = programmed cell death-ligand 1/2, PFS = progression-free survival, RECIST v1.1 = Response Evaluation Criteria In Solid Tumors version 1.1.

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