HERIZON-GEA-01: A Phase 3 Study of Zanidatamab in Combination with Chemotherapy with or without Tislelizumab in First-Line Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Advanced/Metastatic Gastroesophageal Adenocarcinoma (GEA)

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Disclosure of Conflict of Interest

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Background

- GEAs, including gastric, esophageal, and GEJ adenocarcinomas, are common cancers with high morbidity and mortality
- HER2 is overexpressed or amplified in ~20% patients with GEA, and trastuzumab + chemotherapy is the standard of care first-line therapy for these patients in the locally advanced or metastatic setting[1]
- Current median survival for advanced HER2+ GEA remains <2 years[2] and ongoing research with novel agents is attempting to improve outcomes
- Preliminary reports from recent studies suggest that dual targeting of the HER2 and PD-1 pathways may improve upon the results achieved with targeting either HER2 or PD-1 alone[3]

1. Van Cutsem E, et al. *Gastric Cancer*. 2015 Jul;18(3):476-478; 2. Tabernero J, et al. *Lancet Oncol*. 2018 Oct;19(10):1372-1384; 3. Janjigian Y, et al. *Nature*. 2021 Dec;600(7890):727-730.
GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1.

Mechanism of Action of Zanidatamab

- Zanidatamab (also known as ZW25) is a novel, bispecific HER2-targeted monoclonal antibody that binds to two non-overlapping extracellular domains (ECD4 and ECD2) on HER2

- This unique bispecific binding results in multiple mechanisms of action, including formation of HER2 clusters and receptor internalization resulting in downregulation of HER2 on the cell surface, inhibition of growth factor-dependent and -independent tumor cell proliferation, as well as activation of ADCC, ADCP, and CDC[1-3]

1. Weisser N, et al. Data presented at AACR 2021. Abstract 1005; 2. Abraham L, et al. Data presented at AACR 2021. Abstract 1030; 3. Weisser N, et al. Data presented at AACR 2017. Abstract 31.
ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; ECD, extracellular domain; HER2, human epidermal growth factor receptor 2; ZW25, zanidatamab.

Zanidatamab in the Treatment of GEA

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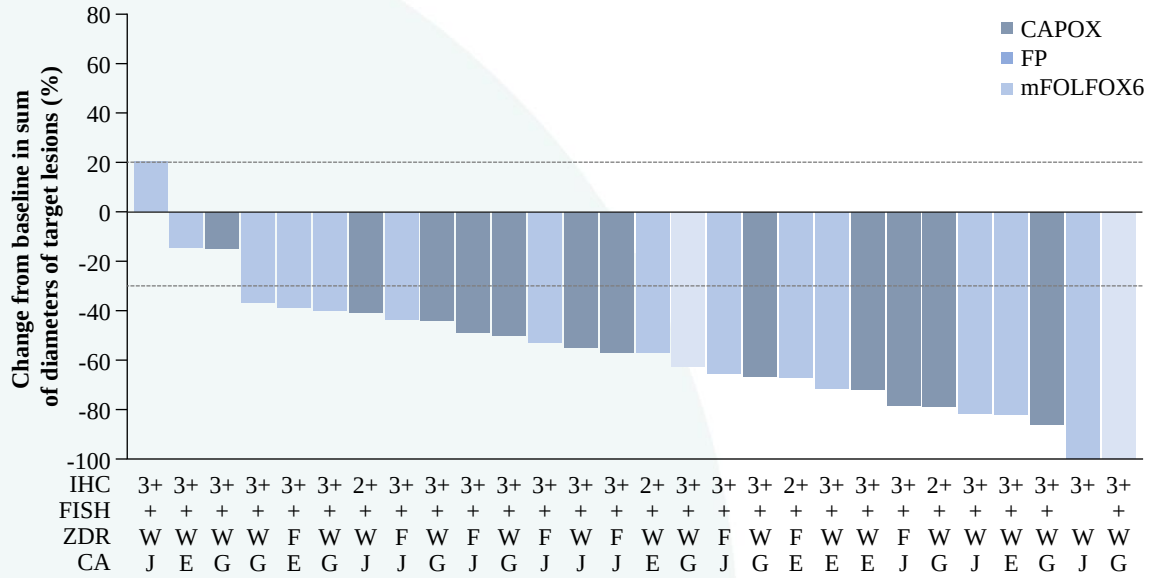
- In early-phase studies, zanidatamab has demonstrated encouraging antitumor activity in HER2-expressing cancers, including HER2+ GEA
- In a phase 2 study in the first-line setting (NCT03929666), preliminary results of zanidatamab + chemotherapy demonstrated a confirmed ORR of 75.0% and a tolerable safety profile[1]

Zanidatamab + Chemo: Efficacy and Safety[1]

	Total patients[a] (N=28)
Confirmed ORR, % (95% CI)	75.0 (55.1, 89.3)
Median DoR, months (range)	16.4 (1.4-19.8+)
Median PFS, months (95% CI)	12.0 (6.9, NE)
Most common TRAEs (in ≥50% patients), n (%)	
Diarrhea	34 (94)
Nausea	27 (75)
Peripheral neuropathy	19 (53)

Data cut off (July 28, 2021).
[a]Efficacy-evaluable population, defined as all HER2+ (IHC 3+ or IHC 2+/ISH+) patients who had ≥1 evaluable post-baseline disease assessment or discontinued study treatment due to death or clinical progression.

Zanidatamab + Chemo: Best Change in Target Lesion Size[1,b]



[b]Per RECIST v1.1 by investigators.

1. Ku G, et al. Data presented at ESMO 2021. Poster 1380P.

5-FU, 5-fluorouracil; CA, primary tumor location; CAPOX, capecitabine + oxaliplatin; CI, confidence interval; DoR, duration of response; E, esophageal cancer; F, flat dosing; FISH, fluorescence in situ hybridization; FP, 5-FU + cisplatin; G, gastric cancer; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; J, gastroesophageal junction cancer; mFOLFOX6, 5-FU + oxaliplatin and leucovorin; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; TRAE, treatment-related adverse event; W, weight-based dosing; ZDR, zanidatamab dosing regimen.

Mechanism of Action of Tislelizumab

- Tislelizumab is a humanized monoclonal antibody against PD-1 that is under clinical development for the treatment of several cancer types

- Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity and competitively blocks PD-L1 and PD-L2 binding, thus inhibiting PD-1-mediated negative signaling in T cells[1,2]

- Tislelizumab was engineered to minimize binding to FcγR on macrophages in order to abrogate ADCP, a potential mechanism of resistance to anti-PD-1 therapy[2]

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1. Labrijn A, et al. *Nat Biotechnol*. 2009 Aug;27(8):767-771; 2. Zhang T, et al. *Cancer Immunol Immunother*. 2018;67(7):1079-1090.
ADCP, antibody-dependent cellular phagocytosis; FcγR, Fc-gamma receptor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2.

Proposed Mechanisms of Action of Zanidatamab and Tislelizumab

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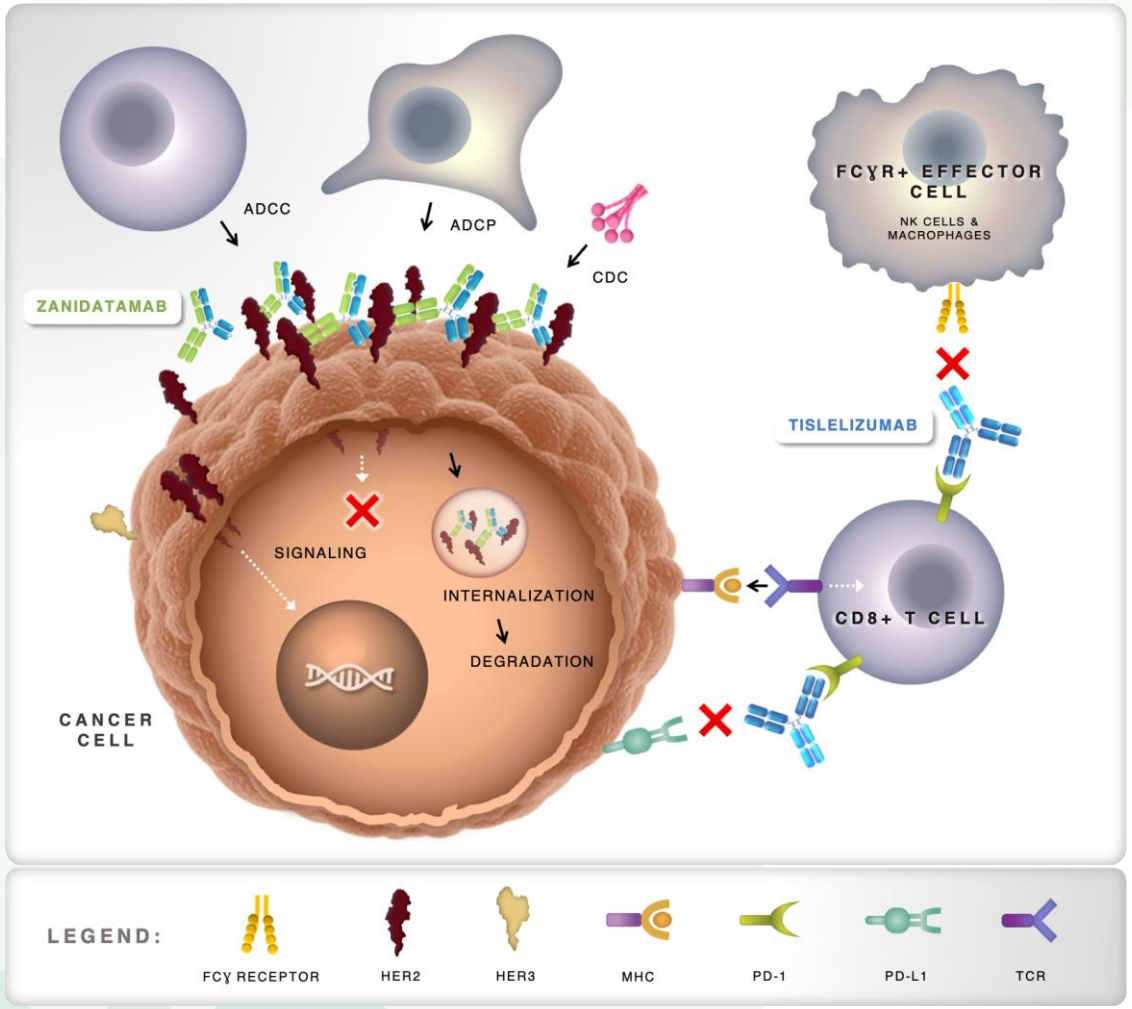
- Zanidatamab and tislelizumab have differentiated and unique mechanisms of action compared with other monoclonal antibodies targeting HER2 or PD-1, respectively

- Zanidatamab binds in *trans* to two non-overlapping domains on separate HER2 proteins, leading to receptor clustering, internalization and downregulation of HER2 on the cell surface, reduction in growth factor-mediated proliferation, as well as activation of ADCC, ADCP, and CDC

- Tislelizumab binds to the extracellular domain of PD-1 and competitively blocks PD-L1 and PD-L2 binding, thus inhibiting PD-1-mediated negative signaling in T cells, minimal FcγRs binding, and abrogates ADCC, ADCP, and CDC effects in humans



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CD8+ T cell, cluster of differentiation 8+ T cell; CDC, complement-dependent cytotoxicity; FcγR, Fc-gamma receptor; HER2, human epidermal growth factor receptor 2; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; T cell, thymus cell (T lymphocyte); TCR, T cell receptor.

Zanidatamab and Tislelizumab in the Treatment of GEA

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- Tislelizumab in combination with zanidatamab and chemotherapy has demonstrated encouraging antitumor activity in HER2+ gastric/GEJ adenocarcinoma
- In a phase 1b/2 trial in the first-line setting (NCT04276493), preliminary results of zanidatamab + chemotherapy + tislelizumab demonstrated a confirmed ORR of 75.8%. Immune-mediated AEs did not affect the overall safety assessment[1]

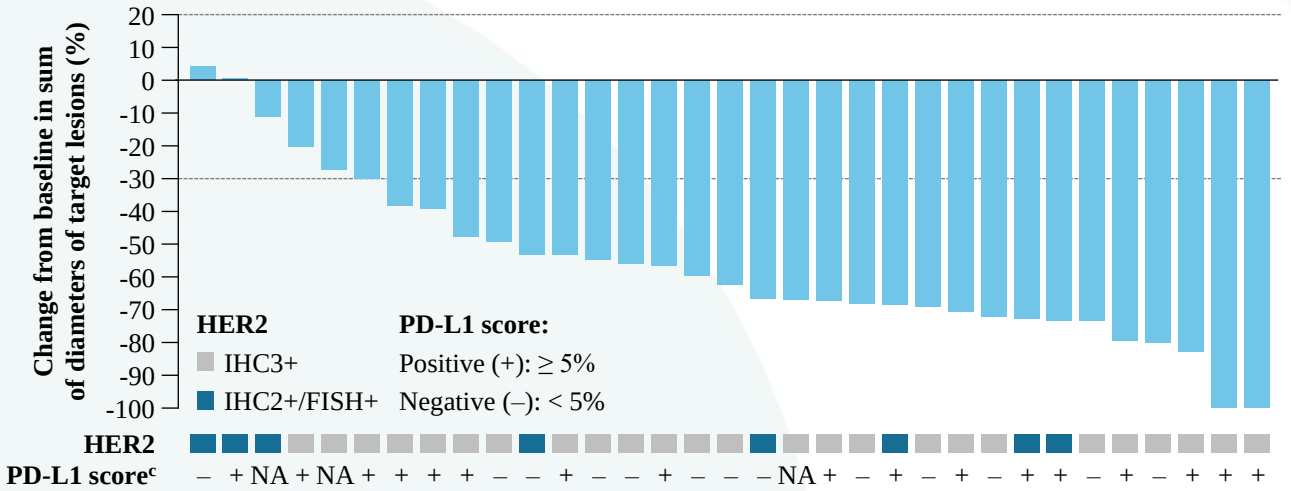
Zanidatamab + Chemo + Tislelizumab: Efficacy and Safety[1]

	Total patients (N=33)
Confirmed ORR, % (95% CI)	75.8 (57.7, 88.9)
DCR, % (95% CI)	100 (89.4, 100.0)
DoR (months), min, max[a]	2.1+, 18.2+
Most common TRAEs (in ≥50% patients), n (%)	
Diarrhea	32 (97.0)
Nausea	21 (63.6)

Data cut off (January 5, 2022).

[a]28% of patients with a confirmed response had DoR events.

Zanidatamab + Chemo + Tislelizumab: Best Change in Target Lesion Size[1,b]



[b]Per RECIST v1.1 by investigators; [c]Assessed by tumor area positive score, which is defined as the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining, and tumor-associated immune cells with PD-L1 staining, at any intensity, as visually estimated using VENTANA PD-L1 (SP263) assay.

Given the encouraging results from early-phase studies, the HERIZON-GEA-01 study will further investigate the efficacy and safety of first-line zanidatamab + chemo ± tislelizumab in patients with advanced/metastatic HER2+ GEA

1. Lee K-W, at el. Data presented at ASCO 2022. Abstract 4032.

AE, adverse event; chemo, chemotherapy; CI, confidence interval; DCR, disease control rate; DoR, duration of response; FISH, fluorescence in situ hybridization; GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NA, not available; ORR, objective response rate; PD-L1, programmed death-ligand 1; TRAE, treatment-related adverse event.

HERIZON-GEA-01 Study

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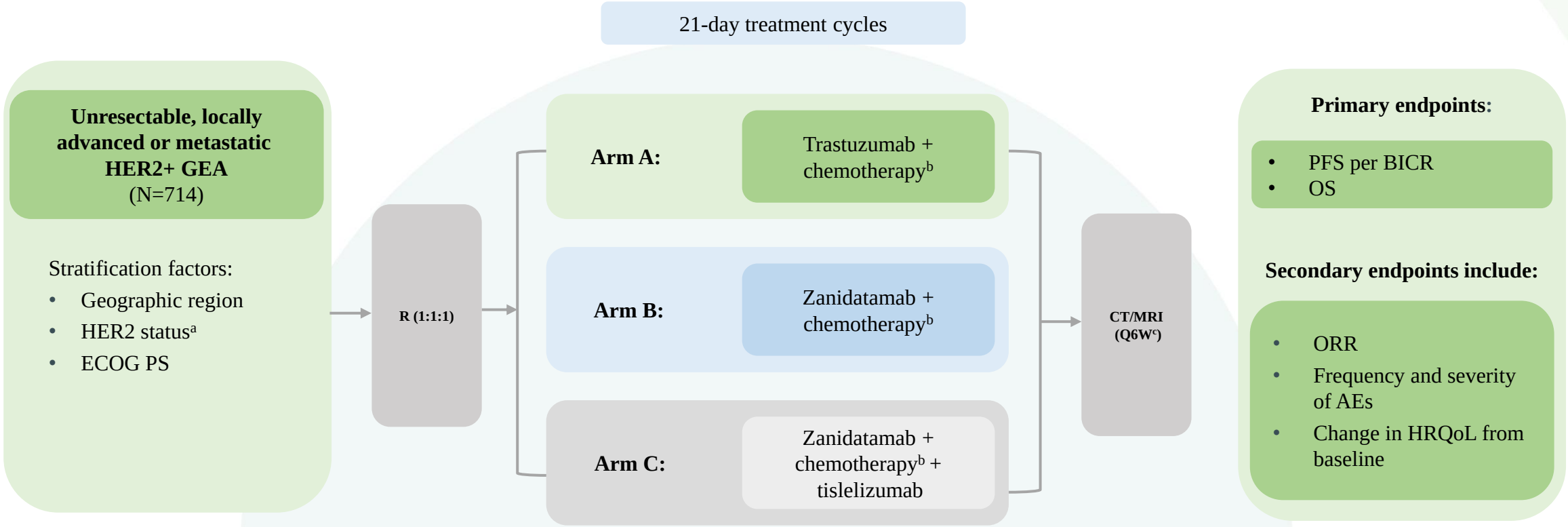
- HERIZON-GEA-01 (NCT05152147; EudraCT#: 2021 000296 36) is a global, randomized, open-label, active-comparator, phase 3 study to evaluate the efficacy and safety of zanidatamab + chemotherapy ± tislelizumab as first-line treatment for patients with advanced/metastatic HER2+ GEA



Patients will be treated until radiographical progression per BICR, clinical progression per investigator, unacceptable toxicity, patient's or investigator's decision to stop, start of subsequent anticancer therapy, lost to follow-up, or death. [a]IHC 3+ or IHC 2+/ISH+; [b]Chemotherapy is physician's choice of either CAPOX or FP; [c]Disease assessments will be done using CT and/or MRI. A baseline scan is required within 28 days of enrollment; subsequent scans are required every 6 weeks for the first 54 weeks and then every 9 weeks thereafter. All scans will be submitted for BICR.

AE, adverse event; BICR, blinded independent central review; CAPOX, capecitabine + oxaliplatin; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; FP, 5 fluorouracil + cisplatin; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IHC, immunohistochemistry; ISH, in situ hybridization; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q6W, every six weeks; R, randomization.

HERIZON-GEA-01 Key Eligibility Criteria and Study Status

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Key inclusion criteria

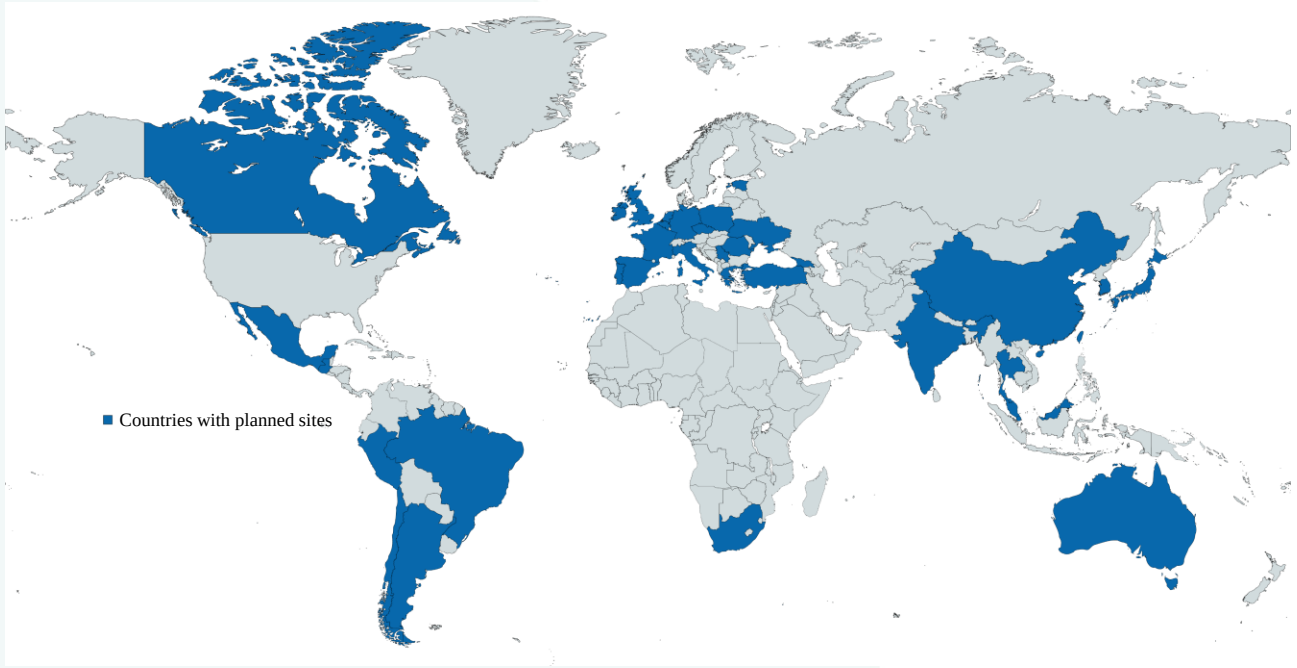
- Age ≥18 years
- Histologically confirmed, untreated, advanced/metastatic HER2+ (IHC3+ or IHC2+/ISH+, per central testing) adenocarcinoma of the stomach, GEJ, or esophagus
- ECOG PS of 0 or 1
- Adequate hepatic, renal and hematologic function
- LVEF ≥50%
- Willing to use acceptable methods of contraception during the study and for a defined period after the study

Key exclusion criteria

- Prior treatment with a HER2-targeted agent
- 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
- Prior treatment with systemic antineoplastic therapy for unresectable locally advanced, recurrent or metastatic GEA. Prior neoadjuvant/adjuvant chemotherapy permitted if completed ≥6 months before enrollment
- Untreated CNS metastases, symptomatic CNS metastases, or radiation treatment for CNS metastases within 4 weeks prior to randomization
- Clinically significant cardiac disease
- Clinically significant pulmonary disease
- Active autoimmune disease

- The HERIZON-GEA-01 study opened to enrollment in November 2021 and is currently recruiting patients
- Recruitment will occur at ~300 sites in more than 30 countries, including 16 sites in the Republic of Korea

Countries with Planned Enrollment Sites



CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LVEF, left ventricular ejection fraction; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2.

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Prior presentation and publication

- The data in this presentation were previously presented at ESMO World Congress on Gastrointestinal Cancer 2022, 29 June–02 July, and has been accepted as a manuscript to *Future Oncology (in press)*.